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Formulation of a novel immediate release heterolithic buccal patch of aspirin

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Abstract

The aim of this work is to prepare an immediate release heterolithic buccal patch of aspirin. Solvent casting method has been used to formulate the fast dissolving buccal patch using FDA approved materials. The use of various excipients for providing optimum patch properties, such as heterolithic nature, super disintegration leading to dissolution of the patch has been analyzed. The problems related to hygroscopicity, disintegration time and residence time have been optimized by varying the excipients. The drug content analysis has been carried out and the patch with 50% sodium starch glycolate (SSG) as a super-disintegrant and 80% lactose as solubility enhancer has shown maximum release of the entire drug content within first 5 min as compared to the one with 30% SSG and 80% lactose. Based on the physicochemical characteristics such as appearance, flexibility, drug content and disintegration, FDAP3 and FDAP4 have been selected for further studies. The *in vitro* studies were carried out and from the drug release profiles, FDAP4 has been considered as the best formulation. From this study, it is apparent that optimum concentration of SSG along with other ingredients are required to produce the required immediate release of sparingly soluble drug like aspirin from buccal patch.

Keywords: Aspirin; Fast Dissolving Buccal Patch; Buccal Drug Delivery System; Sodium Starch Glycolate

INTRODUCTION

Advanced drug delivery systems are developed to improve the drug disposition in the body in order to reduce safety issues and improve the efficacy [1-3]. The physicochemical characteristics of the drug along with their biopharmaceutic, pharmacokinetic and pharmacodynamic properties plays a significant role in designing such drug delivery systems [4]. A number of drug candidates fails to reach the clinic due to the problems raised in the drug development processes such as low aqueous solubility, stability and poor release [5]. Sparingly soluble drugs have numerous formulatory issues based on the route of administration, biopharmaceutical and pharmacokinetic properties [2,6]. This produces local toxicity issues when excess amount of drug is delivered to a local site [2,7]. Ideally, at the site of administration, the drug needs to be swiftly dissolved and distributed over a wide area for minimizing local toxicity and maximizing the absorption [2].

In buccal drug delivery systems, the drug absorption take place through the buccal mucosa and hence directly enters the systemic circulation. Buccal route has several advantages like improving the bioavailability and patient compliance when compared to other routes of administration. It also ensures easy termination of medication upon detachment of the system [8]. Buccal mucosa is highly vascularized in nature and so is the preferred route for attaining faster onset of action since it can bypass first pass effect [9,10]. The volume of saliva in buccal and sublingual region is relatively low, thus the formulation should easily disintegrate [11]. Various BCS class II drugs have been administered through this route [12]. Being a non-steroidal anti-inflammatory drug (NSAID), aspirin plays a major role in the treatment of rheumatoid arthritis, fever and in cardiovascular complications [13]. Aspirin as an anti-platelet agent is being widely explored as a prophylactic against stroke apart from its use as an analgesic [14]. It is a sparingly soluble ester based drug which has the problem of low solubility in aqueous environment [13,15]. For such drugs, formulations with minimum water content need to be prepared for buccal application for maximum stability, in addition for improving the distribution at the site of absorption of drug from the buccal region.

A fast disintegrating buccal patch is most appropriate in this regard [10,16]. The buccal patch with heterolithic structure can be loaded with more amount of drug during dose adjustment. Wherein, the drug will remain phase separated than completely dissolved. Such a heterolithic patch with super-disintegration properties can swiftly disintegrate in the limited salivary volume and distribute the drug over a wide buccal area for absorption. In addition, the film casting process can be adopted in any orphan manufacturing set-up. This study focuses on using sodium starch glycolate (SSG) as a super-disintegrant for aspirin containing fast dissolving heterolithic buccal patch. Where, other formulatory additives are optimized for the successful development of fast-dissolving buccal patch. The study shows that, the SSG concentration needs to be optimized with respect to the concentration of other excipients for obtaining immediate release of the entire drug content within first five minutes.

MATERIALS AND METHODS

Materials

Aspirin, Sodium Lauryl Sulphate (SLS) were purchased from Spectrum Chemicals Pvt. Ltd, Cochin, Kerala. All the chemicals and reagents used were of laboratory grade. The Hydroxy propyl methyl cellulose (HPMC) and Poly ethylene glycol (PEG) 200 were procured from Loba Chemie Pvt. Ltd., sodium starch glycolate (SSG), mannitol, glycerol and propylene glycol from Spectrum reagents and chemicals Pvt. Ltd. Ethanol and methanol were purchased from Nice chemicals Pvt Ltd. All the reagents and buffers were prepared as per standard protocol. The equipment's used were standard UV/ Vis spectrum (SHIMADZU UV-1800 UV VIS Spectrophotometer), dissolution apparatus (Veego, India) and disintegration apparatus (Veego, India). Cellophane membrane (MW cut off 14,000 Da) was purchased from Sigma Aldrich chemicals Pvt. Ltd. and cheek skin (goat) was used.

Methods

Solvent casting method was used to prepare the buccal patch [17]. Required quantity (as shown in Table 2) of HPMC, SSG, mannitol and lactose were dissolved in distilled water with continuous stirring. Air bubbles were removed by the addition of methanol in dropwise manner. Accurately weighed aspirin was dissolved in methanol and slowly added to the polymer solution with continuous stirring. Finally, 0.3ml of PEG 200 was added and stirred. It is kept aside for few minutes. The solution was placed in vacuum oven for 30 minutes and removed the air bubbles. The resulting solution was poured into the propylene glycol coated petri dish and kept in a vacuum oven for 3 hrs. The dried films

were separated and cut into small 1×1cm^2 patches and stored in air tight container until used.

Physico-chemical evaluation of fast dissolving aspirin buccal patch

The resulting patches were characterized for physical properties, drug content uniformity, drug permeability, disintegration time, drug release and kinetic modelling & *ex vivo* studies for residence time.

Physical evaluation, weight variation, thickness and folding endurance

Visual inspection of all patches were performed for color, smoothness and flexibility. For that, patches (1cm x 1cm^2) (n=3) from each set were weighed on a digital balance and the average weight was calculated. Thickness of the patches was measured by using micrometer screw gauge and mean values were determined. Folding endurance was evaluated by folding a strip of patch at the same area repeatedly until a crack was observed [18].

Determination of drug content

Aspirin buccal patch of size (1cm x 1cm) (n=3) allowed to dissolve in phosphate buffered saline (PBS) having pH 6.8 under occasional shaking in a volume of (10ml) for half an hour. At definite time intervals, 1ml of sample solution was withdrawn and made up to 10 ml with PBS. Amount of drug present in each patch were determined by UV spectrophotometer, using PBS as blank [18,19].

Disintegration time and ex vivo residence time of prepared fast dissolving aspirin patch

Disintegration time was determined using standard disintegration apparatus. Disintegrating time is defined as the time (seconds) at which a film disintegrates when it come in contact with water or saliva. A buccal patch of size 1×1cm^2 was placed inside the disintegration apparatus filled with pH 6.8 buffer maintained at 37±0.5°C and the time taken for the patch to disintegrate was noted down. For *ex vivo* residence time, goat cheek skin was purchased from local abattoir. The ex-vivo residence time was determined by using locally modified USP disintegration apparatus. The disintegration medium consists of simulated solution of saliva of pH 6.8, maintained at temperature 37±0.5°C. A piece of buccal patch was dipped into phosphate buffer and calcium chloride solution. The patch was glued to surface of mucosa (goat cheek skin) which was kept in the apparatus and allowed to move up and down so that the patch was completely immersed in and out of the buffer solution. The time taken by the patch to detach from the mucosal surface was recorded, the average of three readings was taken for analysis [20].

In vitro dissolution study of buccal patch

The amount of drug released from aspirin buccal patch with respect to time was studied by using type-1 (Basket type) USP apparatus. Buccal patch (1×1cm^2) was placed in the basket and release studies were done in PBS (pH 6.8) (500ml) dissolution medium. The apparatus was maintained at a temperature of 37±0.5°C and rotated at 100 rpm. A quantity equivalent to 5ml of sample was withdrawn at various time intervals (0, 5, 10, 15, 20, 25min) and the same amount of buffer was replaced after each interval and analyzed spectrophotometrically at λ max 265nm [18].

Kinetic modelling

The data obtained from the drug release studies of the buccal patch was fitted to various models such as Zero order, First order, Higuchi model and Korsmeyer-Peppas model to determine the mechanism of drug release. The plots were drawn and the regression equations were obtained for each plot. The model with the highest correlation coefficient (r^2 value approaching unity) was chosen as the best fit model [8,21]. The equations for the various kinetic models are as depicted below.

Zero order: $Q_t = Q_o + K_o t$

First order: Log Q_t = Log Q_o + $K_1 t$ / 2.303

Higuchi : $Q = K_H t^{1/2}$

Korsmeyer – Peppas: $Q_t = Kptn$

From the equations, K_0 and K_1 represents the zero and first-order rate constants. **Q** denotes the fraction of drug release at time **t**. K_H and K_p represents the Higuchi and Korsmeyer-Peppas rate constants respectively. The release mechanisms were analyzed based on "**n**" value (diffusion constant) obtained from the Korsmeyer-Peppas model: Fickian (n≤ 0.5), Case II transport (n≥1) and Non-Fickian (n value in between 0.5 and 1) [8,22].

Permeability study of fast dissolving aspirin patch

Magnetic mixer was used to conduct the permeability studies. Aspirin buccal patch of 1×1cm^2 was placed into a cellophane bag (MW 14000 Da) containing 1ml PBS (pH 6.8) (releasate), tied both the ends, and placed in a beaker containing 50ml of PBS (pH 6.8) (acceptor compartment) and stirred using a magnetic stirrer at 37°C and 50 rpm. Sample solutions were withdrawn from the acceptor compartment at predetermined time intervals and replaced the same volume with fresh buffer. The aliquots of samples were examined spectrophotometrically at λ max 265nm. The concentration of drug was calculated and plotted against time [23].

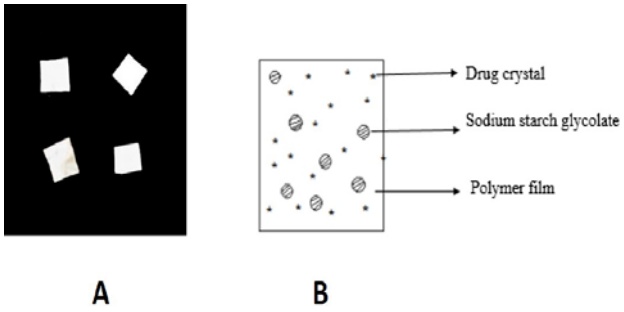

Figure 1. (A) Aspirin containing buccal patch and (B) Schematic illustration of the buccal patch

Table 1. Preformulation studies for the of development of aspirin containing buccal patch

Ingredients	Trial 1	Trial 2	Trial 3	Trial4
Aspirin	+	+	+	+
HPMC	+	+	+	+
SLS	+	+	+	-
Mannitol	+	+	+	+
Glycerol	+	-	-	-
Propylene glycol	-	+	+	+
Ethanol	+	+	+	-
Methanol	-	-	-	+
Water	+	+	+	-
SSG	-	+	+	+
PEG 200	-	-	-	+

RESULTS AND DISCUSSIONS

Selection of buccal patch

For initial optimization (Table 1) of the composition of the buccal patch, various excipients are considered including SLS. Initial batches were hygroscopic. Incorporation of glycerol in the formulation is suspected to be the primary reason for the hygroscopicity. In the 2nd trial, glycerol is substituted with propylene glycol (Table 1). Also lactose is introduced in the formulation in order to improve the disintegration time of the patch. In addition, SSG is added in varying concentrations. The patches obtained from trial 2 are consistent and free from hygroscopicity, but disintegration time of patch is not satisfactory

(53sec). In the third trial, the only notable change is in the concentration of lactose in order to improve the disintegration time of the patch. Disintegration time are improved by changing the concentration of lactose from 60% to 80% of HPMC and this composition is further fine-tuned, hereto forth, known as Fast Dissolving Aspirin Patch (FDAP).

Table 2. Optimization of composition of aspirin containing buccal patch

Ingredients	FDAP1	FDAP2	FDAP3	FDAP4
Aspirin (mg)	312.5	312.5	312.5	312.5
HPMC (mg)	500	500	500	500
PEG200 (ml)	0.3	0.3	0.3	0.3
Mannitol (mg)	50	50	50	50
Lactose (mg)	300	300	400	400
SSG (mg)	90	150	120	200

For that, the concentration of SSG is changed with respect to concentration of lactose (Table 2). In FDAP1 and FDAP2, the lactose concentration is 60% of that of polymer (Table 2). In the optimized patches FDAP3 and FDAP4, the lactose concentration is increased to 80% of that of the polymer, along with increase in SSG concentration (Table 2). The patches FDAP 1 & FDAP 2 obtained are consistent and free from hygroscopicity (Table 3).

Physico-chemical evaluation of aspirin buccal patch

The results of the physicochemical evaluation are given in table 3. The optimized patches are opaque, non-sticky, smooth and moderately flexible (Fig.1 A) and the schematic illustration of the patch is given in Fig. 1 (B). The individual weights and thickness (Table 4) of the patches are found to be consistent among the samples of a particular trial. However, between the formulations, the weight and thickness increased with increase in solid content (SSG) of the formulation. The folding endurance (Table 4) of the patches FDAP3 and FDAP4 decreased with the increase in content of lactose as it reduces the flexibility of the buccal patch. The folding endurance of the optimized patch is carried out and both the patches broke into two halves with single complete folding; while it is moderately flexible. It shows that, the said patch cannot be used in areas where flexibility is an issue. Rather it can be used in the region between gum and buccal region similar to that of buccal tablets are being placed.

Drug content

The drug content analysis (Table 4) showed that FDAP 3 has low drug content than FDAP 4, i.e. 820 µg for FDAP 3 and 1200 µg FDAP 4. This is because in this work unit area is compared not in terms of matrix, and there is difference in thickness. Further, weight equated studies are planned.

Dissolution study

In vitro drug release studies (Fig. 2) in phosphate buffer of pH 6.8 (simulated pH of saliva) showed that drug release increased with the increasing content of SSG. This is visible in both rate and extent, hence a maximum release of 97.91% (FDAP4) and 82.31% (FDAP3) is obtained. The higher release is attributed to the rapid disintegration property of SSG, resulting in increased penetration of water into the patch, and hence, increased diffusion of the drug. The HPMC is also responsible for the swelling, as it enhances disintegration of the patch and dissolution of the drug.

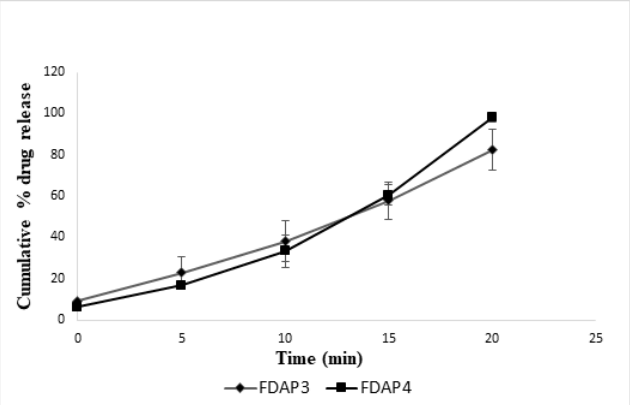

Figure 2. Percentage drug release of FDAP 3 and FDAP 4

Table 3. Physicochemical properties of prepared fast dissolving aspirin buccal patches

Formulation code	Flexibility	Smoothness	Transparency	Stickiness
FDAP 1	Not Flexible	Smooth	Opaque	Non-sticky
FDAP 2	Not Flexible	Smooth	Opaque	Non-sticky
FDAP 3	Not Flexible	Smooth	Opaque	Non-sticky
FDAP 4	Not Flexible	Smooth	Opaque	Non-sticky

Table 4. Summarized data of formulations FDAP 3 & FDAP 4

Code	Weight variation (mg)	Thickness (mm)	Folding endurance (No :)	Drug content (µg)	Disintegration time (sec)	Ex-vivo residence time (Sec)	Percentage drug release (%)
FDAP 3	11.8433±0.557	0.01733±0.0152	1	820	13	10	82.31
FDAP 4	20.4393±0.3867	0.03631±0.0141	1	1200	10	5	97.91

Table 5. Kinetic analysis data of *in vitro* drug release from aspirin containing buccal patch

Release model		Formulation code	
		FDAP3	FDAP4
Zero order	R^2	0.9853	0.9450
	k	3.6585	4.5375
First order	R^2	0.9611	0.6912
	k	0.1099	0.1370
Higuchi	R^2	0.6331	0.5260
	k	18.4138	21.7002
Korsmeyer-Peppas	R^2	0.9775	0.9540
	k	9.8918	6.8117
	n	0.7113	0.8865

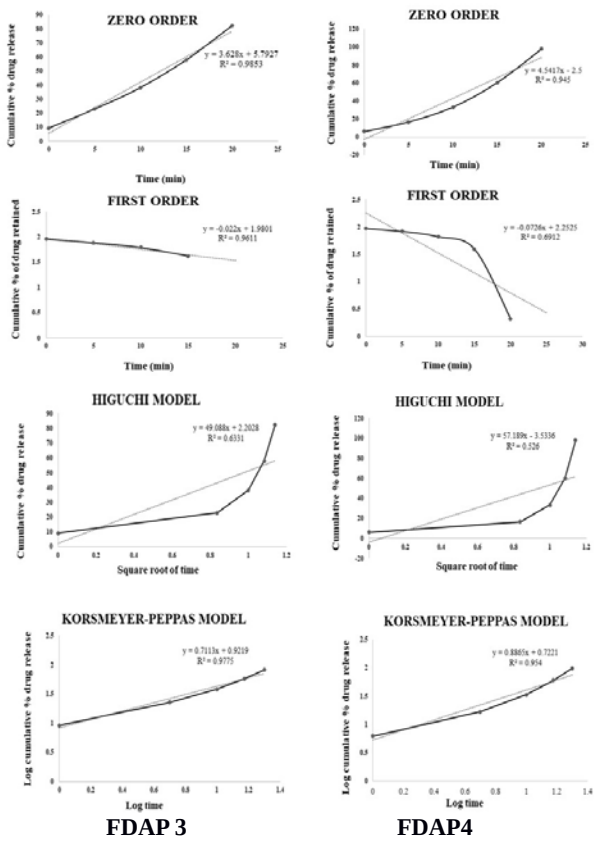

Figure 3. Kinetic modelling of FDAP 3 and FDAP 4

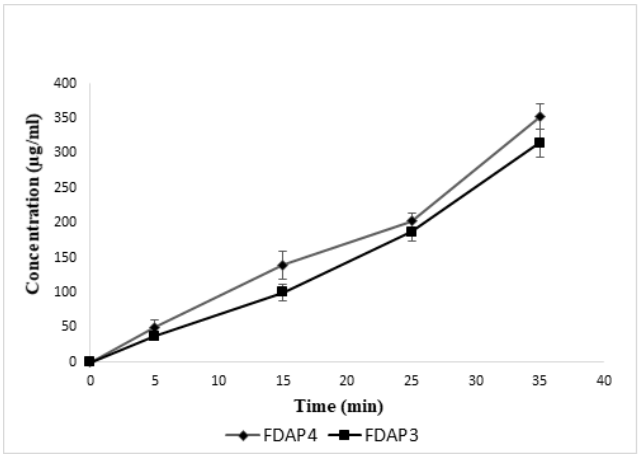

Figure 4. Drug permeability of FDAP 3 and FDAP 4

Disintegration test and ex vivo residence time

The disintegration time (Table 4) is found to be 13 seconds for FDAP 3 and 10 seconds for FDAP4 this is due to increase in SSG concentration. Ex-vivo study is carried out and residence time (Table 4) of both the patches is found to be 10 seconds and 5 seconds for FDAP 3 and FDAP 4 respectively. The reduced residence time is due to rapid disintegration. This is attributed to the fact that the rapid uptake of water by SSG brought about the disentanglement of the polymer chains with gradual reduction in mucoadhesive bonding.

Kinetic modelling

The mechanistic analysis of drug release profile has shown (Fig. 3 and Table 5) that upon comparison of FDAP3 & FDAP4 drug release follows Zero order and Korsmeyer-Peppas model dependency. However, they differ in its dependency on First order kinetics. Wherein, FDAP4 is first order dependent while FDAP3 is independent and the drug release rapidly increases after certain point, indicating that there exists a difference in heterogeneity of the drug reservoir between these two formulations. Thus further studies are planned in that direction.

Permeability of aspirin buccal patch

From Fig.4, FDAP4 showed increased drug permeation compared to FDAP3. This is due to increased content of SSG and lactose as well as overall high drug content in FDAP4, resulting in rapid dissolution and availability of the drug in the solution.

CONCLUSION

The drug delivery through buccal mucosa using buccal patch is an alternative route to oral drug delivery system such as tablets, capsules, which overcome the limitations such as degradation due to gastric acids, intestinal enzymes, gastric irritation and hepatic first pass effect. Buccal mucosa helps in rapid absorption of drug, giving optimum pharmacological effect. For that, faster drug release from the dosage form is required and is achieved hereby developing a fast disintegrating buccal patch. Aspirin is formulated as buccal patch by solvent casting method using sodium starch glycolate (SSG) as superdisintegrant; allowing its faster disintegration. Other additives used in the formulation were PEG200 (plasticizer), HPMC (polymer), lactose (disintegrant & solubility enhancer) and methanol (solvent). Aspirin undergoes hydrolysis in water and so it is replaced with methanol to overcome this problem. Based on the physicochemical characteristics, drug content, drug release and disintegration time; FDAP3 and FDAP4 is selected for further studies. The drug release studies are done for this formulation and from the results between FDAP3 & FDAP4; the FDAP4 is the best formulation because of faster disintegration due to increased concentration of SSG. In the present study SSG is used as a formulatory additive for enhancing the disintegration and dissolution of buccal patch. Wherein, its concentration is optimized with lactose and other ingredients for getting a heterolithic patch with fast drug releasing properties. Future studies are planned for dosage form optimization with respect to required drug content, weight and thickness of the patch need to be done. Further, the suitability of this patch to develop as a unit solid dosage form also need to be assessed.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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