Formulation and Evaluation of Novel Unidirectional Release Buccal Tablet of Diclofenac Sodium

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Abstract

The purpose of the proposed study was to develop a unidirectional release buccal tablet which releases the drug in one direction and in a controlled manner. Various approaches including matrix tablet of drug with mucoadhesive polymers, triple layer reservoir system and peripheral coating of mucoadhesive polymer were adopted for the design of unidirectional release buccal tablet (URBT). Many mucoadhesive polymers, e.g., HPMC K4M, Carbopol, PVP K30, and Polycarbophil (Noveon AA1) were tried to achieve satisfactory mucoadhesion and predetermined drug release. Out of those, the peripheral coating of 50 mg Polycarbophil on a core tablet containing 50 mg diclofenac sodium, 10 mg HPMC, and spray dried lactose was optimized for a successful design of URBT. To mimic the one-directional drug release from URBT, a USP-II apparatus was modified, and a new device was fabricated, which mimicked unidirectional release. This novel controlled release design was evaluated for *in vitro* drug release study, *ex vivo* mucoadhesion study, *in vitro* drug permeation study, surface pH, and swelling index. The optimized batch (A11) of URBT was subjected to a short-term stability study. The FTIR spectrum and stability study data revealed a stable characteristic of the formulation. The *in vitro* dissolution data of URBT were treated by household model fitting software 'FORTRAN' which showed the URBT follows the Korsmeyer and Peppas model of drug release kinetics. This controlled and unidirectional release of diclofenac sodium through the buccal mucosa is superior to all other buccal formulations of diclofenac sodium.

Keywords: unidirectional release, buccal tablet, modified dissolution apparatus, diclofenac sodium, short-term stability study.

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Introduction

Recent years have seen enormous advances in the field of peptide and protein engineering by means of biotechnology and recombinant technology, and today there are various possibilities that a significant number of biologically active peptides and proteins are therapeutically applicable. In most cases, such compounds are intended for chronic therapy, where they will need to be administered by an appropriate delivery system. Currently, all possible alternative routes of peptide and protein administration, avoiding the parenteral route, are being investigated with great effort, both in industry and academia. They include the nasal, transdermal, pulmonary, rectal, buccal, vaginal, ocular, and peroral routes and, for each route, a special drug delivery system has been or is being designed (Junginger, Hoogstraate et al. 1999).

The oral mucosa can be categorized into sublingual, gingival, and buccal mucosa through which transmucosal delivery can be achieved. The absorption of therapeutic agents from the oral cavity provides a direct entry of such agents into the systemic circulation, thereby avoiding the first-pass hepatic metabolism and gastrointestinal degradation. However, the buccal route of drug delivery has received much more attention because of its unique advantages

over other oral transmucosal routes (Desai and Kumar 2004).

The conventional buccal adhesive tablets have some limitations: conventional tablets may not have a uniform adhesive layer, leading to weak adhesion; and because of non-uniform adhesive and backing layers, the release of the drug may not be unidirectional (Remuñán-López, Portero et al. 1998).

Diclofenac sodium is a potent nonsteroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis and other rheumatic disorders. Diclofenac sodium is an example of a drug which is subjected to first-pass metabolism since only 50–60% of the drug reaches the systemic circulation in the unchanged form. Moreover, peroral administration of diclofenac sodium results in gastrointestinal disturbances ranging from abdominal discomfort, nausea, and vomiting to serious gastrointestinal bleeding or peptic ulcers (El-Samaligy, Yahia et al. 2004).

Technically, an ideal buccal adhesive system must have the following 3 properties maintains its position in the mouth for a few hours, releases the drug in a controlled fashion and provides drug release in a unidirectional way toward the mucosa.

In regard to the first requirement, strong adhesive contact of the system with buccal mucosa can be established if a system having a uniform adhesive surface is prepared using appropriate combinations of the mucoadhesive polymers. In addition to that, by selecting the optimum ratio of a similar polymer or combination with other release retardant polymers, the second requirement can be fulfilled. The third requirement can be achieved by designing a system having a uniform adhesive and backing layer. Therefore, the first step in the development of a buccal device is the selection of an appropriate adhesive. A number of bioadhesive polymers have been investigated for buccal purposes, mainly polycarbophil, carbopol, hydroxyl propyl methyl cellulose, and polyvinylpyrrolidone. When hydrated with water, these polymers adhere to the oral mucosa, withstanding salivation, tongue movement, and swallowing for a significant period of time.

The main aim of the present study was to develop a unidirectional release buccal tablet (URBT) of diclofenac sodium. Various approaches were tried for the formulation of URBT, including matrix tablet, triple layer reservoir system, and peripheral coating of the mucoadhesive polymer at the core of the tablet containing diclofenac sodium. Furthermore, various mucoadhesive polymers along with release retardants and release enhancers were tried to achieve satisfactory mucoadhesion and a controlled drug release profile. The investigation also includes modification of the USP-II dissolution apparatus for a more realistic in situ assessment of the release of drugs from URBT. The release profiles of diclofenac sodium from the URBT were evaluated in-vitro and the formulation that gave the best results has been submitted to preliminary long-term and short-term accelerated stability tests. *In vitro* dissolution study data were subjected to drug release model fitting software FORTRAN.

Experimental

Materials

Diclofenac sodium was a gift from Lincoln Pharmaceuticals (Ahmedabad, India). Ethyl cellulose was received as a gift sample from Signet, Mumbai. Polycarbophil (Noveon AA1) was a gift from Noveon, Inc., USA. Hydroxy propyl methylcellulose (HPMC) K4M was provided by Colorcon Asia Pvt. Ltd., Goa. Spray-dried lactose was supplied by Intas Pharma (Ahmedabad, India).

Tablet Preparation

The preparation of URBT involves two steps: (1) the formation of the core and (2) the formation of URBT. All ingredients were passed through an American Society for Testing Materials (ASTM) sieve no.100 and blended separately in a mortar. The core tablet was prepared using the Cadmach single punch tablet machine (Cadmach, Ahmedabad, India). The punching machine, equipped with 10.36 mm flat-faced punches and dies, was used for preparing the core tablet. Then the core tablet was placed in a 12.85 mm die cavity and the required quantity of polycarbophil was added at the periphery. Finally, the remaining portion of the die was filled with ethyl cellulose and compressed using a 12.85 mm flat-faced upper and lower punch to obtain URBT. In addition to this approach, various other approaches were tried, including mucoadhesive polymer in drug matrix and a triple layer reservoir system to formulate URBT. The

proposed designs of various approaches to URBT are shown in figures 1(a), 1(b), and 1(c). The composition of various designs of URBT is shown in Tables 1-3.

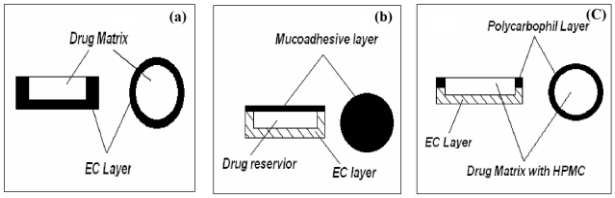

Fig.1 URBT with (a) mucoadhesive polymer within drug-polymer matrix (b) triple layer reservoir system (c) peripheral mucoadhesive coating

Table 1. Formulation batches containing matrix system

Excipients	A1	A2	A3	A4	A5	A6
DS	50	50	50	50	50	50
HPMC	50	50	25	15	15	15
Polycarbophil	50	25	50	50	50	50
SDL	100	125	125	131.5	133	134.75
NaCl	--	--	--	3.5	--	--
SSG	--	--	--	--	2	--
PEG-4000	--	--	--	--	--	1.25
Mg. sterate (%)	1	1	1	1	1	1
Talc (%)	2	2	2	2	2	2

(DS= Diclofenac sodium, SDL= spray deried lactose,SSG = sodium starch glycolate,)

Table 2. Formulation batches containing Triple layer reservoir system

Layer	Excipients	A7	A8	A9
Mucoadhesive layer	HPMC	10	10	10
	Polycarbophil	10	20	20
	PVP	10	10	20
Reservoir	DS	50	50	50
	SDL	150	140	130
Protective layer	EC	180	180	180

Table 3. Formulation batches containing Peripheral mucoadhesive coating

Layer Excipients		A10	A11	A12
Peripheral Mucoadhesive layer	Polycarbophil	50	50	50
Core tablet	HPMC	0	10	20
	DS	50	50	50
	SDL	150	145	140
Protective layer	EC	180	180	180

Evaluation of Physical Properties of URBT

URBTs were examined for weight uniformity, thickness uniformity, hardness, and friability. The obtained values of these properties were then compared with the values of the limits stated in the Indian Pharmacopoeia for conventional oral tablets.

Swelling Studies

URBTs (n=3) were weighed individually (designated as W_1) and placed separately in Petri dishes containing 4 mL of phosphate buffer (pH 6.6) solution. At regular intervals (0.5, 1, 2, 3, 4, 5, and 6 hours), the URBTs were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen URBTs were then reweighed (W_2) and the swelling index (SI) was calculated using the following formula (Desai et. al; 2004).

$$SI = \frac{(W_2 - W_1)}{W_1} \times 100$$

In Vitro Drug Release Study

The drug release rate was determined using a modified USP dissolution apparatus II. The tablet from each batch was adhered by cyanoacrylate adhesive to the flat surface of the device shown in fig 2. The dissolution medium (900 ml phosphate

buffer pH 6.8) was maintained at 37±1^{0}C and stirred at 50 rpm. At the end of predetermined time intervals (e.g., 1, 2, 3, 4,5 and 6 h), aliquots (5 mL) were removed from each dissolution vessel and filtered. An equal volume of drug-free medium (5 mL) to that of the aliquot removed was replaced in each dissolution vessel to maintain a constant volume of the medium during the dissolution test. The percentage of drug released at each time point was quantified by ultraviolet spectroscopy at a λ^{max} of 276 nm with a total of three replicate determinations for each batch.

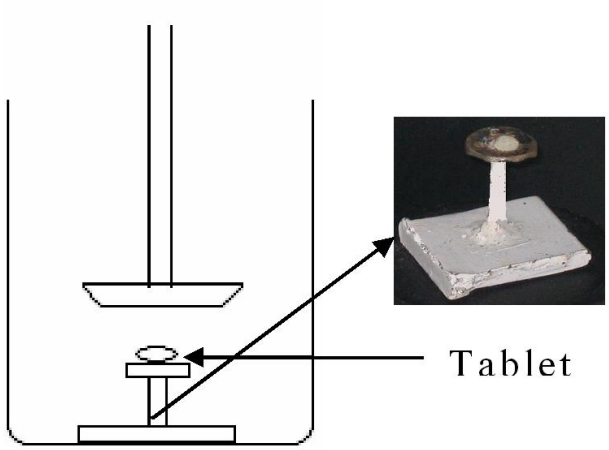

Fig 2. Modified USP-II Apparatus

A tensiometer was used to study the mucoadhesion force of URBT. A rat buccal mucosa was used as a model for the buccal membrane. The epithelium was separated from the underlying connective tissues with surgical scissors and affixed to the platform of the tensiometer with adhesives. The test batches of URBT were applied to the buccal mucosa. A force was applied to the URBT manually for 30 sec to adhere the URBT to the buccal mucosa. The URBT was attached to the wire hook of the tensiometer, and force was applied to detach the URBT from the mucosa. The readings noted down from the dial were in dynes (6–8).

Surface pH

A combined glass electrode was used for this purpose. Three tablets for each batch were allowed to swell by keeping them in contact with 1.0 ml of simulated saliva fluid for 2 hours, and pH was noted by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1.0 minutes (Khanna, Agarwal et al. 1996).

In Vitro Drug Permeation Study

An *in vitro* permeation study of diclofenac through the Guinea pig buccal mucosa was performed using Franz-type diffusion cells at 37°C ± 0.2°C. The tissue was stored in Krebs buffer at 4°C upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between the donor and receiver chambers of the Franz-type diffusion cell. The temperature was maintained at 37°C ± 0.2°C by a jacket surrounding the receiver chamber that was stirred with a magnetic bead. After the buccal membrane was equilibrated with Krebs buffer solution between both chambers, the receiver chamber was filled with phosphate buffer (pH 6.8), and the donor chamber was charged with diclofenac URBT. Aliquots (5 mL) were collected at a preset time (every hour for 6 hours) and filtered, and the amount of diclofenac permeated through the buccal mucosa was then determined by measuring the absorbance at 276 nm using a UV spectrophotometer. The dissolution medium of the same volume (5 mL), which was prewarmed at 37°C, was then replaced in the diffusion cell. The experiments were performed in triplicate (n = 3) (Ceschel, Maffei et al. 2001).

Stability Study

In the present work, stability studies were carried out for selected formulations at room temperature (25±2°C/60±5%RH) and accelerated temperature (40±2°C/ 75±5%RH) for 3 months. The samples were maintained in close amber glass bottles. The general appearance, organoleptic properties, dissolution profile, mucoadhesion strength, and drug content of the tablets were determined after 3 months.

Model Fitting

The method of Bamba et al. was adopted to ascertain the kinetics of drug transport. Different kinetic models were used to analyze the data from optimized batch A11 and to evaluate the transport mechanism of diclofenac sodium. FORTRAN software, developed in-house, was used. The least value of the sum of squares of residuals (SSR) and Fisher's ratio (F) was used to select the most appropriate kinetic model (Bamba, Puisieux et al. 1979).

Result and Discussion

In Vitro Drug Release

The main aim of this study was to develop a novel unidirectional release buccal tablet of diclofenac sodium. The design was expected to provide drug delivery in a unidirectional fashion to the mucosa and to avoid loss of drug due to washout by saliva. Polycarbophil was selected as the bioadhesive polymer because of its extremely interesting properties. On the other hand, EC, being hydrophobic, has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility. As per the prime requirement of controlled release, the therapeutic level of the drug should be achieved in the initial period. Fast release of drugs should be required in the initial period for some specific categories of drugs (antimigraine drugs, pain killers, antianginals, etc.).

Various approaches were tried for the formulation of a unidirectional release buccal tablet: Matrix tablet in which the mucoadhesive polymer was matrixed with drug and filler and the matrix core tablet was protected with ethyl cellulose coating on three sides. Triple layer reservoir system, in which a bilayer (core) tablet was prepared to contain two layers, one of drug with filler and the upper layer was only of mucoadhesive polymer. Finally, the core tablet was coated with ethyl cellulose. The third approach was a peripheral coating of mucoadhesive polymer. The ring of the mucoadhesive polymer was prepared at the periphery of the core tablet containing the drug, filler and release controlling polymer. Finally, the core tablet was coated with ethyl cellulose.

The first batch of tablets was prepared on the hypothesis of the mucoadhesive strength of a co-mixture of HPMC K4M and Polycarbophil with a ratio of 50:50. Batch A1 satisfied the mucoadhesion but failed to achieve the predetermined drug release. The ideal buccal dosage form should provide t90% within 6-8 hrs. The formulations (A1-A3) revealed only 40% drug release after 6 hrs. The reason behind this is the massive nature of the gel formed by HPMC/Polycarbophil due to water uptake.

The approach of adding hydrophilic compounds (polyethylene glycol, sodium chloride, and mannitol) and disintegrating agents (sodium starch glycolate) was adopted. The logic behind this was to enhance pore formation in the gel structure through which the drug may diffuse at a higher rate.

In URBT, the swelling was restricted to one surface only. Since the remaining three surfaces were coated with ethyl cellulose. So, the swelling was only in the axial direction, rather than a radial and axial swelling in a simpler unprotected matrix tablet of HPMC. The drug was found to be released from the upper surface of the swelled polymer. When the matrix URBT was observed after 6 hrs, the inner part of the matrix remained intact without any treatment by media. The addition of hydrophilic polymers or sodium starch glycolate did not exhibit a significant effect on drug release. So, the approach of matrixing the drug with bioadhesive polymer failed.

Drug particles present on the surface of the matrix are initially released into the surrounding media, generating many pores and cracks that facilitate the further release of the drug. To accelerate the drug release from the matrix tablet system, the approach of a porous tablet was also adopted. To increase the pores in the matrix tablet, camphor was included in the matrix. Since camphor is a sublimable excipient, it was tried. The logic behind this was to generate pores by the sublimation of camphor. The prepared tablet, after compression, was put into a drier to volatilize the camphor. The concentrations of camphor were tried at 1%, 2%, and 5%. The cumulative percentage of drug release after 6 hrs was found 21.83, 22.80 and 25.11 respectively for 1%, 2% and 5% of camphor. However, the increased amount of camphor did not show any remarkable effect on the drug release.

When we consider the oral delivery of diclofenac sodium, the lower solubility of diclofenac sodium at pH 1.2 limits the initial release of surface drugs as well as the formation of channels within the matrix. Consequently, the overall release of diclofenac sodium has decreased. The initial lag period of 2 hrs is due to the acidic nature of diclofenac sodium. The drug, being a weak acid (pKa 4.0), is practically insoluble in acidic solutions but dissolves readily in intestinal fluid and water.

The second approach of the triple-layer reservoir system was adopted by considering the diffusion of the drug through a much-thickened layer of mucoadhesive polymer. As shown in the Fig 1(b) the upper layer of the tablet was made up of

bioadhesive polymer, a middle layer of drug and filler, and an outer layer of ethyl cellulose which can cover the core tablet by keeping one surface open for drug release and adhesion.

The main important parameter which controls the drug release is the thickness of the upper layer. The thickness of the upper layer was kept to a minimum so that the drug could easily pass out of the reservoir. On the other hand, the low amount of upper layer composition blend caused tabletting problems since a uniform layer was difficult to achieve with a low amount of polymer blend.

By considering the results of matrix URBT, the blend of the mucoadhesive upper layer was prepared by varying the ratio of HPMC, Polycarbophil, and Polyvinyl Pyrrolidone (PVP). Because of its hydrophilic nature, with high solubility and mucoadhesion power, PVP was incorporated into the blend.

In the initial stage, the dissolution of PVP created channels in the gel network which could fasten the drug release. But it failed to obtain a predetermined result. The lag time for drug release was found in such a system. An initial couple of hours are required for the wetting of the upper layer, which swells and makes a gelling structure. Once the channels open in the gelling structure because of the dissolution of PVP, the medium enters the middle layer and helps to diffuse the drug.

For diffusion to occur, the first step is the wetting of the drug with water, followed by its dissolution so that the drug molecule is available in a molecular form to diffuse out of the matrix. Hence, the net release rate observed is a cumulative effect of the drug's solubility (influenced by its structure, molecular weight, and pKa), polymer properties (hydrophilicity/lipophilicity, molecular weight, and tortuosity) and the relative ratio of drug and polymer in the tablet**.**

Many scientists have worked to determine the release characteristics of diclofenac from different bioadhesive polymers, and they have found that the diclofenac sodium release rates from the different bioadhesive systems can be arranged in descending order as follows: Cp974p~SCMC> Na alginate > polycarbophil > PEO>HPMC> Xanthan gum HPC. Thus, Cp974p, polycarbophil, PEO, and SCMC have shown optimum adhesion properties and diclofenac release patterns. So, these polymers or their combinations may be useful for the formulation of diclofenac URBT.

To date, there is no official method available for the in-vitro dissolution of the buccal dosage forms. Various scientists have adopted different methods for the evaluation of drug release by mimicking the buccal conditions. For example, Dor and Fix developed a special disintegration test using a texture analyzer instrument to accurately determine the rate of drug release from sublingual and buccal tablets. In this method, the tablet is attached to a cylinder probe and placed under a constant force to promote disintegration (Dor, Fix et al. 2000). Ikinei et al. used an alternative method to study the release of nicotine from the buccal tablet. They used modified Franz diffusion cells for this purpose (Ikinci, Şenel et al. 2004). Mumtaz and Ch'ng introduced another method for assessing the dissolution of the buccal tablet. The device that they have fabricated is based on the circulation of a per-warmed dissolution medium through a cell (Mumtaz and Ch'ng 1995). Cilurzo et al. have coated all the surfaces of buccal tablets except one using a water-impermeable coating to mimic the intended drug release from one surface only (Cilurzo, Minghetti et al. 2003).

In the present study, for the dissolution test of URBT, the problem occurred when the dissolution was carried out in the USP Apparatus-II without any modification. This was because of the adherence of the tablet to the walls of the dissolution vessel. Since only one side of the tablet is exposed to dissolution media, there might be a chance of the complete hindrance of drug release for a couple of minutes when the free side is adhered to the wall. This happened sometime after the exposure of tablets to the media. That lag time is because of the time required for the swelling of the polymers and that gelling adhesive mass to stick to the wall of the vessel. This caused a problem in the assessment of the in vitro drug release of URBT.

To overcome this problem and to mimic the proper condition, a Teflon-coated device was developed, on which the upper side has a platform to fix the URBT (figure.3). The device was put in the USP Apparatus-II without disturbing the vortex of the media. The distance

between the paddle and the device was kept at 25±2 mm as per the dissolution guideline.

Since the tablet was coated on three sides, swelling was found on one side only, and the appearance of the swellable tablet seemed to be concave swelling. After 6 hrs, only the hollow cavity of EC remained, which indicates that the swellable gel of polymer eroded with time by the movement of dissolution media and that part of the drug was released. After the total removal of drug-polymer content from the inner cavity, only a hollow cylinder of EC remained.

From the results of the matrix and triple layer reservoir tablets, it is concluded that, in the formulation of URBT, to achieve satisfactory mucoadhesion and predetermined controlled release, the bioadhesive layer and release controlled polymer layer should be discriminated.

So, the approach of peripheral coating of bioadhesive polymer at the periphery of the core tablet containing drug, filler, and release controlled polymer was adopted. Since, in this design of URBT, there is no interference of bioadhesive polymer in releasing a drug. Both these criteria will be fulfilled by two different parts of the tablet. From the primary study optimization of polycarbophil, it was observed that at 50 mg of polycarbophil, satisfactory bio adhesion could be achieved. The amount of polycarbophil was kept at 50 mg, which was feasible for compression. On the other hand, considering the composition of a core tablet, the drug, spray dried lactose, and varying concentrations of HPMC were tried. Taking into consideration that HPMC is also a bioadhesive polymer and the bio adhesion of URBT was achieved by the contribution of both polycarbophil and HPMC, though polycarbophil was significantly responsible for bio adhesion, because the polycarbophil layer directly comes into contact with buccal mucosa rather than HPMC, which required time for swelling and at that minimum concentration could not achieve strong mucoadhesion.

In this, the design first trial was done without the incorporation of HPMC in the core tablet. The results revealed that since the core tablet contained only the drug with filler, there was no control over the drug release. 90% of drugs were released within 1 h. To control the drug release, HPMC K4M was incorporated with varying concentrations of 10% and 20%. Batch A12 containing 20% HPMC in the core tablet showed release retardation. Batch A11 containing 10 % HPMC exhibited predetermined control on drug release rate and was considered an optimized batch and subjected to further study. The dissolution profiles of URBT batches are shown in Fig 3.

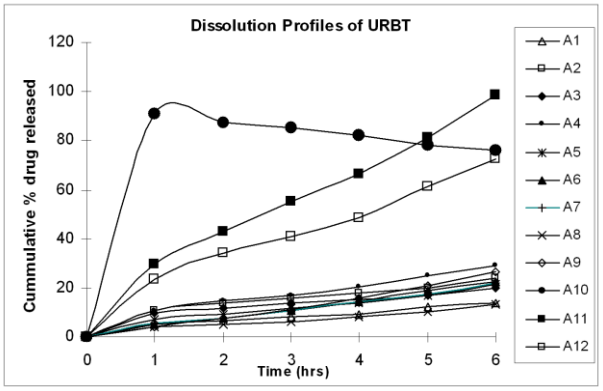

Fig 3. In Vitro Dissolution Profiles of URBT batches (A1-A12)

Ex-Vivo Mucoadhseion Study

The bioadhesive forces of the URBTs are affected by the shape of the tablet, the swelling degree of the tablet, and the nature of the tablet components. The large and flat tablets have a stronger bioadhesive force as compared to the small and concave tablets due to the wide surface area for binding to the buccal mucous membranes.

The swelling capacity of the tablet components contributed greatly to the swelling degree of the tablet. Hydrophilic components have a stronger bioadhesive force compared to hydrophobic components due to their high swelling capacity. Since buccal mucous membranes consist of oligosaccharide chains with sialic acid, polymers with hydrophilic groups such as carboxyl and hydroxyl groups can bind strongly in a strong bioadhesive force. Therefore, in the development of the diclofenac URBT, the bioadhesive force is important in finding the condition that allows the proper attachment of the tablet to the human buccal mucosa.

To select the bioadhesive polymer suitable for the diclofenac URBT, the tablets were prepared by the various aforementioned approaches and by varying the ratio of different bioadhesive polymers. Hydroxy propyl methyl cellulose

(HPMC), Carbopol, polycarbophil and Polyvinyl Pyrrolidone were selected as the bioadhesive polymers. These bioadhesive polymers are water soluble or swellable, but of a different nature. HPMC, a cellulose derivative, is neutral and swells in water. Carbopol, a polycyclic acid derivative polymerized without a cross-linking agent, is anionic and water swellable. Polycarbophil, a cross-linking agent, is also an anionic salt that swells in water. The bioadhesive forces of URBTs were not dependent upon the shape of the tablet, since it was fixed in the flat form, 12.85 mm in diameter.

Adhesion occurs shortly after the beginning of hydration and swelling, but the bonds formed are not very strong. Excessive hydration may result in the formation of slippery, noninvasive mucilage, thus decreasing adhesive strength or even resulting in loss of adhesion. This is also probably a result of the dilution of functional groups available for adhesive interaction at the interface between the bioadhesive system and mucus.

Noveon AA1 (polycarbophil) is a homopolymer of acrylic acid cross-linked with divinyl glycol. The high molecular weight polycarbophil readily swells in water and in biological fluids. Considering the first approach of matrixing a mucoadhesive polymer with drug and filler, HPMC and polycarbophil, both contributed to the bio adhesion effect. Since both polymers can swell in the presence of water and biological fluid, there will be an entanglement of the polymer chains and then, after interaction of the chains with the mucous network, On the other hand, with this ratio of bioadhesive polymers, predetermined drug release was not achieved. So, the composition of the bioadhesive polymer was changed and decreased up to the minimum level at which it can give proper bio adhesion. The optimised ratio of bioadhesive polymer was found to be 15mg and 50 mg for polycarbophil and HPMC, respectively. Since it was found that the polycarbophil significantly decreased the drug release as compared to the HPMC, on accounting for this, HPMC content was kept constant and polycarbophil content was reduced till proper mucoadhesion was achieved.

Most hydrophilic polymers can absorb water and swell. This can increase the ability to adhere to mucosal surfaces. Because PVP has a high-water solubility that critically limits its application as an effective mucoadhesive polymer, hydration leads to the formation of a gel that starts to disintegrate due to dissolution. This leads to slippery mucilage and a loss of adhesive properties. On the other hand, HPMC is a nonionic polymer containing only hydroxyl groups, which can form weak hydrogen bonds with mucous layers. Furthermore, due to its slow rate of hydration, it can form a strong surface gel that efficiently adheres to the mucosal surface and remains in contact for a longer time.

It was found that the bioadhesive polymers differ in their adhesion properties and can be arranged in descending order as follows: Polycarbophil >Cp974p > PEO~ Xanthan gum >SCMC>Na alginate ~ HPMC~HPC. The high bioadhesive strength of polycarbophil and Cp974p may be due to the formation of secondary bio adhesion bonds with mucin due to their rapid swelling and interpenetration of the polymer chains in the interfacial region, while the other polymers only undergo superficial bio adhesion.

Surface pH and Swelling Index

The surface pH of all formulations was found to be within an acceptable range of neutral pH and hence, these formulations did not cause any irritation in the buccal cavity**.** The swelling index was found to be dependent on the polymer content. Out of selected bioadhesive polymers (HPMC, Carbopol, Polycarbophil, and PVP), HPMC exhibited a higher swelling rate (Fig. 4)

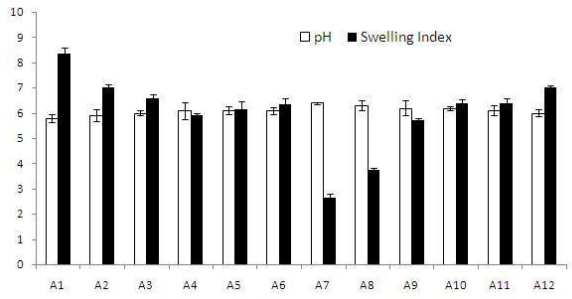

Fig 4. Swelling index and pH of URBT batches (A1-A12)

Model Fitting

The *in vitro* drug transport data of batch A11 were analyzed for establishing the kinetics of drug transport. Model fitting was done using an in-house program developed by the authors. Zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, and Weibull models were

tested. The best fit was shown by the Korsmeyer-Peppas model with the least sum of squares of residuals (SSR = 77.911) and Fischer's ratio (F = 19.477). The mechanism of transport was by anomalous diffusion (diffusion coefficient, n = 0.6561) (Table 4).

Table 4. Model fitting data of Optimized URBT

DRUG RELEASE KINETICS DATA			BATCH
Sr. no.	**Kinetic Model**	**Parameters**	**A11**
1	Zero order	SSR	142.846
		F	28.5692
		Corr. Coeff.	0.9890
		R^2	0.9781
2	First order	SSR	4867.011
		F	973.402
		Corr. Coeff.	-0.8543
		R^2	0.7298
3	Higuchi	SSR	232.129
		F	46.425
		Corr. Coeff.	0.9820
		R^2	0.9820
4	Hixon-Crowell	SSR	542.057
		F	108.411
		Corr. Coeff.	0.9408
		R^2	0.8850
5	Korsmeyer and Peppas	SSR	77.911
		F	19.4777
		Corr. Coeff.	0.9926
		R^2	0.9853
6	Weibull	SSR	331.912
		F	82.9782
		Corr. Coeff.	0.919
		R^2	0.845

Stability Study

The infrared spectroscopy of diclofenac sodium and URBT were determined to identify the drug and to assess the compatibility of the drug with excipients and conditions used for the preparation. Overlaid FTIR spectra of diclofenac sodium and URBT are shown in Fig 5. The peaks obtained at 767.62, 745.40, 1284.50, 1305.72, 1469.52, 2970.17, and 3396.77cm^{-1} showed the characteristic peaks of diclofenac sodium, which revealed the drug-excipient compatibility in URBT (Swain, Nagamani et al. 2015).

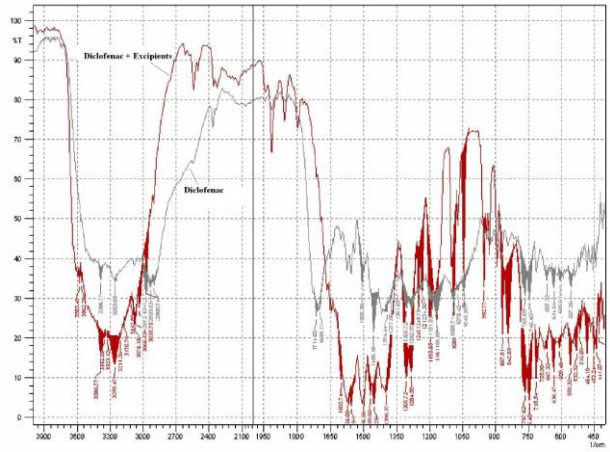

Fig 5. Overlaid FTIR spectra of diclofenac sodium with URBT

Conclusion

The novel approach of peripheral coating of Polycarbophil (50 mg) on the core tablet of diclofenac sodium, HPMC (10 mg), and spray dried lactose exhibited successful controlled and unidirectional buccal delivery of diclofenac sodium. The modification in the USP-II apparatus simulated unidirectional release in the buccal cavity. The short-term stability data demonstrated the stability of the formulation. The URBT formulation followed the Korsmeyer-Peppas model of drug release kinetics.

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