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Article

Design and evaluation of dental pastes Containing anti-inflammatory drugs

Nadeem Hasan[1], Amit Kumar Nayak[2], Syed Sanaullah[1], Farheen Sami[3], Shahnaz Majeed[3], Vishal Bhagwan Badgujar[3], Saquib Hasnain[4], Mohammed Tahir Ansari[*,3,5]

[1]Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga, India, [2]Department of Pharmaceutics, Seemanta Institute of Pharmaceutical Sciences, Mayubhanj, India, [3]Faculty of Pharmacy and Health Sciences, Universiti Kuala Lumpur Royal College of Medicine Perak, Ipoh, Malaysia, [4]Department of Pharmacy, Shri Venkateshwara University, Amroha, India,[5]School of Pharmacy, University of Nottingham Malaysia, Jalan Broga, Semenyih, Malaysia

Periodontitis is an oral disease associated with inflammation and pain with swollen and bleeding gums. In the present study, dental pastes containing NSAIDs, namely, diclofenac sodium and nimesulide (1 % w/w) were prepared to treat periodontitis. Dental pastes of diclofenac sodium and nimesulide (1 % w/w) were prepared with/without mucoadhesive hydrocolloid polymers such as sodium carboxy methyl cellulose (NaCMC), hydroxyl ethyl cellulose (HEC) and methyl cellulose (MC) by conventional trituration method. The pH, drug content, viscosity, tube spreadability and tube extrudability of these prepared dental pastes were measured. These dental pastes of diclofenac sodium and nimesulide (1 % w/w) were characterized by FTIR analyses for drug-excipient compatibility. The *in vitro* drug releases from these dental pastes in 6.4 pH phosphate buffer solution displayed sustained release over longer period and the drug release rate was found to be decreased when the concentration of mucoadhesive polymer was increased. These dental pastes displayed good adhesion to the oral mucosa revealing more retention time in mouth when tested for *ex vivo* mucoadhesion using bovine cheek pouch. The stability study results reveal that the DC3 and NC3 dental paste formulations were found stable enough over a longer period in different storage conditions. The present study revealed that the prepared mucoadhesive dental pastes of diclofenac sodium and nimesulide (1 % w/w) had good adhesion with the oral mucosa to maintain consistent release of drugs over prolonged time.

Keywords: Periodontitis. Nimesulide. Diclofenac. Mucoadhesive.

INTRODUCTION

Periodontitis is an oral disease affecting a significant proportion of people in all groups, races, ethnicities and genders (Barat *et al*., 2007; Patel, Patel, 2013). The early stage of periodontal disease leads to a painful suffering associated with swollen and bleeding gums (Pataquiva Mateus, Ferraz, Monteiro, 2007). If untreated, it can destroy both bone and soft tissues that support teeth and eventually may produce tooth loss (Ferraz *et al*., 2007; Lindhe, Haffaiee, Socransky, 1983; Seymour, Heasman, Macgregor, 1992). Historically, the etiology of periodontitis has focused on the bacterial plaque, microbial by-products, and the host immune response (Lindhe, Haffaiee, Socransky, 1983). Bacterial plaques are considered as the primary etiologic factor of periodontitis (Seymour, Heasman, Macgregor, 1992). The current periodontitis treatment includes the delivery of anti-inflammatory drugs and antibiotics (Ali *et al*., 2012; Barat *et al*., 2007; Ferraz *et al*., 2007; Pataquiva Mateus, Ferraz, Monteiro, 2007; Patel, Patel, 2013; Seymour, Heasman, Macgregor, 1992). Recently, various local drug delivery approaches to treat periodontitis have been investigated to reduce the side-effects associated with systemic drug administration for a

***Correspondence:** M. T. Ansari. *School of Pharmacy University of Nottingham Malaysia. Jalan Broga, Semenyih 43500. Selangor, Malaysia.* Email: md.a.tahir@unikl.edu.my. Tahir.Ansari@nottingham.edu.my. Phone: 0060174914594

longer period (Barat *et al*., 2007; Barat *et al*., 2006; Ferraz *et al*., 2007). Local delivery systems for the treatment of periodontitis have some potential limitations and benefits. If applied as a monotherapy, then the troubles related with the local drug delivery to treat periodontitis may comprise allergic reactions, possible incapability to disrupt bio-films and also, may malfunction to remove the calculus (Lindhe, Haffaiee, Socransky, 1983; Seymour, Heasman, Macgregor, 1992). The benefits comprises of the ease of application, selectively targeting a limited number of diseased-sites that are unresponsive to the conventional therapy, and possibly improves the treatment results at specific locations (Barat *et al*., 2006). The present work was designed to improve the gel hardness, spreadability and compressibility, properties that may affect the ease of product removal from the container (Barat *et al*., 2006; Killoy, 1998).

Earlier, medical researchers hypothesized that the production of prostaglandins and other metabolites of arachidonic acid locally within the periodontitis infected tissues usually contributes to the alveolar bone resorption (Etienne, 2003). Recent medical research findings on periodontitis have shown that the inhibitors of prostaglandin production, like non-steroidal anti-inflammatory drugs (NSAIDs) could affect the course of tooth bone loss in periodontal infection (Jones, Woolfson, Brown,1997). Even these findings indicate that NSAIDs can reduce the gingival inflammation and reduce the alveolar bone resorption (Ahmed *et al*., 2009). The utility of medicated paste formulations containing NSAIDs for the topical drug delivery have been found more economical towards both patient's choice and the industrial point of view than the other existing marketed formulations. Most of the hydrophilic macromolecules or hydrocolloids forming polymers contains numerous hydrogen bond forming groups, these hydrogen forming groups has the tendency to consolidate mucoadhesion. The mucoadhesiveness of the polymeric membrane is achieved in two stages, the first stage involves initiation of contact between the biological membrane and the polymer and the second stage involves consolidation of the polymer initiated by weak vanderwaal's forces and hydrogen bonding (Ali *et al*., 2010; Carvalho *et al*., 2010). In the present study, an attempt has been made to prepare and evaluate dental pastes containing NSAIDs, namely, diclofenac sodium and nimesulide (1 % w/w). Diclofenac sodium and nimesulide are two widely used NSAIDs having analgesic, antipyretic and anti-inflammatory activities (Soskolone, Freidman, 2004; Williams, *et al*., 1989). Diclofenac sodium is an inhibitor of prostaglandin synthesis (Soskolone, Freidman, 2004) whereas nimesulide specifically inhibits cyclooxygenase-2 thus exerting milder effects on the gastrointestinal mucosa (Williams *et al*., 1989). Therefore, the aim of the current research was to prepare and evaluate mucoadhesive dental pastes containing diclofenac sodium and nimesulide (1 % w/w) for the possible use in the treatment of periodontitis.

MATERIAL AND METHODS

Material

Diclofenac sodium and nimesulide were obtained from B. S. Traders Pvt. Ltd., India. Precipitated chalk (calcium carbonate), sodium carboxy methyl cellulose (NaCMC; molecular weight of 262.19 g/mol), hydroxyl ethyl cellulose (HEC; molecular weight of 736.71 g/mol) and methyl cellulose (MC; molecular weight of 658.73 g/mol) were obtained from LobaChemie Pvt. Ltd., India. Glycerin, methyl paraben, camphor, potassium dihydrogen orthophosphate, sodium lauryl sulfate (SLS) and sodium hydroxide were obtained from SD Fine Chemicals, India. Methanol (Raxil-Ranbaxy, India), cellophane membrane (Himedia Laboratories Pvt. Ltd., India) and empty aluminum collapsible tubes (Digvijay Containers & Closures, India) were used. Demineralized and double distilled water was used. All other chemicals and reagents used were of analytical grade.

Preparations of dental pastes

Dental pastes of diclofenac sodium (1 % w/w) and nimesulide (1 % w/w) were prepared by conventional trituration method. Hydrocolloids and methyl paraben were mixed in measured quantity of water and glycerin with the help of a mortar and pestle. Drugs (1 % w/w diclofenac sodium or nimesulide) were dissolved in remaining quantity of water and added to the above

mixture with continuous trituration for 30 minutes. Previously sifted (75 # sieve) precipitated chalk (calcium carbonate) was gradually added to the above mixture followed by camphor. The trituration was continued until smooth paste was obtained. The formulation charts of various dental pastes containing diclofenac sodium (1 % w/w) or nimesulide (1 % w/w) are shown in Table I and Table II, respectively.

TABLE I - Formula of various diclofenac sodium (1 % w/w) dental pastes

Formulation codes	DA1	DA2	DA3	DB1	DB2	DB3	DC1	DC2	DC3	DX
Calcium carbonate (g)	42.50	42.00	41.50	42.50	42.00	41.50	42.50	42.00	41.50	44.00
Glycerine (g)	28.00	28.00	28.00	28.00	28.00	28.00	28.00	28.00	28.00	28.00
MC (g)	1.50	2.00	2.50	-	-	-	-	-	-	-
HEC (g)	-	-	-	1.50	2.00	2.50	-	-	-	-
NaCMC (g)	-	-	-	-	-	-	1.50	2.00	2.50	-
Methyl paraben (g)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Camphor (g)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
SLS (g)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Diclofenac sodium (% w/w)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Water qs to 100 g	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

TABLE II - Formula of various nimesulide (1 % w/w) dental pastes

Formulation codes	NA1	NA2	NA3	NB1	NB2	NB3	NC1	NC2	NC3	NX
Calcium carbonate (g)	42.50	42.00	41.50	42.50	42.00	41.50	42.50	42.00	41.50	44.00
Glycerine (g)	28.00	28.00	28.00	28.00	28.00	28.00	28.00	28.00	28.00	28.00
MC (g)	1.50	2.00	2.50	-	-	-	-	-	-	-
HEC (g)	-	-	-	1.50	2.00	2.50	-	-	-	-
NaCMC (g)	-	-	-	-	-	-	1.50	2.00	2.50	-

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Formulation codes	NA1	NA2	NA3	NB1	NB2	NB3	NC1	NC2	NC3	NX
Methyl paraben (g)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Camphor (g)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
SLS (g)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Nimesulide (% w/w)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Water qs to 100 g	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

Determination of drug content uniformity

Dental pastes (1 g each) of diclofenac sodium and nimesulide were dissolved in methanol. The solutions were suitably diluted and the absorbance were measured at 278 nm for diclofenac sodium and 297 nm for nimesulide against the appropriate blanks using a UV-VIS Spectrophotometer (Shimadzu Corporation, Japan).

pH determination

Dental pastes (1 g each) of diclofenac sodium and nimesulide were taken in a 150 ml beaker. 10 ml of freshly boiled and cooled water (at 27°C) was added. These mixtures were stirred to make thorough suspension. The pH of the suspension was measured within 5 min using digital pH meter (Systronics Instruments, India).

Viscosity measurement

The viscosities of formulated diclofenac sodium and nimesulide dental pastes were determined using Brookfield viscometer (DV-III Units Programmable Rheometer, USA) at a controlled temperature of 30 ± 5ºC.

Tube spreadability measurement

Formulated diclofenac sodium and nimesulide dental pastes (1 g) were weighed at the centre of the glass plate (10 x 10 cm) and another glass plate was placed over it carefully. Weight of 2 kg was placed at the centre of the plate to avoid sliding of the plates for each formulation. The diameters for each dental paste were measured after 30 min.

Tube extrudability measurement

The dental pastes of diclofenac sodium and nimesulide were filled in clean lacquered aluminum collapsible one-ounce tubes with a nasal tip of 5 mm openings. The pressure on these aluminum collapsible one-ounce tubes was applied by the help of finger. The tube extrudability for all these dental pastes were determined by measuring the percentage amount of pastes extruded through the tip when a pressure was applied on tube paste.

Fourier transform-infrared (FTIR) spectroscopy analyses

Samples were mixed with potassium bromide (KBr) and analyzed as KBr pellets by using a FTIR spectroscope (Perkin Elmer Spectrum RX I, USA). The pellet was placed in the sample holder and spectral scanning was taken at a resolution of 4 cm^{-1} with scan speed of 1 cm/sec.

In vitro drug release studies

Drug release of the diclofenac sodium and nimesulide from various medicated dental pastes (1 g

each) was studied by using the permeation apparatus. A glass cylinder with both the ends open, 10 cm in height, 3.7 cm in outer diameter and 3.1 cm in inner diameter was used as a permeation cell. A cellophane membrane soaked in distilled water (24 h before use) was fixed to the end of the cylinder with aid of an adhesive to result the permeation cell. 1 g of medicament was kept in permeation cell. A beaker of containing 100 ml of 6.4 pH phosphate buffer solution was used as the receptor compartment. The sample was immersed to a depth of below the surface of medium in the receptor compartment. The medium in the compartment was agitated using a magnetic stirrer at the temperature 37± 1ºC. Samples were withdrawn (5ml) at the interval of 15 min and assayed at 278 nm for diclofenac sodium and 297 nm for nimesulide against the appropriate blanks using a UV-VIS Spectrophotometer (Shimadzu Corporation, Japan).

Mucoadhesive test

A modified physical balance composed of a two-arm balance was used to evaluate the mucoadhesive performances of these dental pastes. The left arm of the balance was replaced by small stainless steel lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane. Bovine mucosal membrane was used as model mucosal membrane for the mucoadhesive test.

The bovine buccal mucosa excised from bovine cheek pouch was obtained within 2 h of its death from the slaughter house and immediately transported to the laboratory in 6.4 pH phosphate buffer solution. The buccal mucosa was separated from the full thickness of the tissue after immersion in distilled water and then in 6.4 pH phosphate buffer solution, at 37 ± 1°C for 2 min. The fatty layers were removed by scalpel, and the buccal mucosa was isolated from the underlying tissue. Finally, the mucosa was washed with 6.4 pH phosphate buffer solution.

The excised and washed bovine buccal mucosa was fixed to the movable platform. 1 g of dental pastes was fixed to the stainless steel lamina using glue. The exposed paste surface was moistened with 1 ml of 6.4 pH phosphate buffer solution for 30 sec for initial hydration and swelling. The platform was then raised upward until the hydrated pastes were brought into contact with the mucosal surface. A preload of 20 g weight was placed for the evaluation of each paste over the stainless steel lamina for 3 min as initial pressure, and then weights were slowly increased on the right pan, till the pastes detach from the mucosal membrane. The weight required (in g) to detach the paste from the mucosal membrane was measured as the mucoadhesive strength (shear stress) of these dental pastes (Amit, 2010).

Stability studies

The stability studies of selected dental pastes were performed in accordance to the International Conference on Harmonization (ICH). The selected diclofenac sodium and nimesulide dental pastes (1 g each) were subjected for stability studies for a period of 4 weeks. These selected dental pastes were packed in the collapsible tubes and stored at refrigeration (5°C ± 1°C) temperature for 1 h and at 45°C ± 2°C, under 70 ± 5 % relative humidity (RH) for 4 weeks. The drug content, pH, spreadability and extrudability were determined for each selected dental pastes tested for their stability.

Statistical analysis

All data was analyzed with simple statistics. The simple statistical analysis was conducted using MedCalc software version 11.6.1.0.3.

RESULTS

In the present work, dental pastes of diclofenac sodium and nimesulide were formulated using MC or HEC or NaCMC in three different concentrations with varying concentration of calcium carbonate (Table I and Table II). Glycerin was used as humectants and co-solvent. Methyl paraben, SLS and camphor were used as preservative, surfactant and flavoring agent, respectively. The dental pastes of diclofenac sodium

(1 % w/w) were found white and sticky. On the other hand, the dental pastes of nimesulide (1 % w/w) were found to be yellowish. The pH of diclofenac sodium (1 % w/w) dental pastes was found within the range, 5.86 to 6.96 (Table III). The pH of nimesulide (1 % w/w) dental pastes was found within the range, 6.56 to 6.86 (Table III). The diclofenac sodium (1 % w/w) dental pastes showed drug contents within the range, 96.43 ± 1.82 to 99.51 ± 3.93 % (Table III). The drug contents (1 % w/w) nimesulide dental pastes were found to be within, 96.43 ± 1.74 to 99.63 ± 3.74 % (Table III). The viscosities of diclofenac sodium (1 % w/w) dental pastes were measured within the range, 40065.08 to 65259.92 cps (Table III) and for nimesulide (1 % w/w) dental pastes were measured within the range, 40056.25 to 65261.02 cps (Table IV).

The tube spreadability of (1 % w/w) diclofenac sodium and nimesulide dental pastes was measured within the range, 6.10 ± 0.58 to 7.45 ± 0.63 cm and 6.63 ± 0.44 to 7.53 ± 0.26 cm respectively (Table III). The tube extrudability of diclofenac sodium and nimesulide (1 % w/w) dental pastes was measured within the range, 86.07 ± 2.86 to 96.39 ± 2.73 % and 83.48 ± 0.96 to 96.27 ± 3.26 % respectively (Table III).

The FTIR spectrum of diclofenac sodium exhibited peak absorption bands at 3383 cm^{-1} and 3259 cm^{-1} corresponding to N–H and weak C–O–H absorption, respectively. Presence of aromatic ring was confirmed by strong C=C absorption appeared at 1574 cm^{-1} and 1557 cm^{-1}. All these characteristic peaks of diclofenac sodium appeared without any significant shifting in the FTIR spectrum of formulated diclofenac sodium (1 % w/w) dental pastes (Figure 1). The FTIR spectrum of pure nimesulide exhibited strong peak at 3283 cm^{-1} corresponding to N–H of the sulfonamide. At 1598 cm^{-1} and 1588 cm^{-1}, further presence of aromatic C=C absorption was observed. At 1153 cm^{-1}, the S=O absorption peak was noticed. All these characteristic peaks of nimesulide appeared without any significant shifting in the FTIR spectrum of formulated nimesulide (1 % w/w) dental paste (Figure 2)

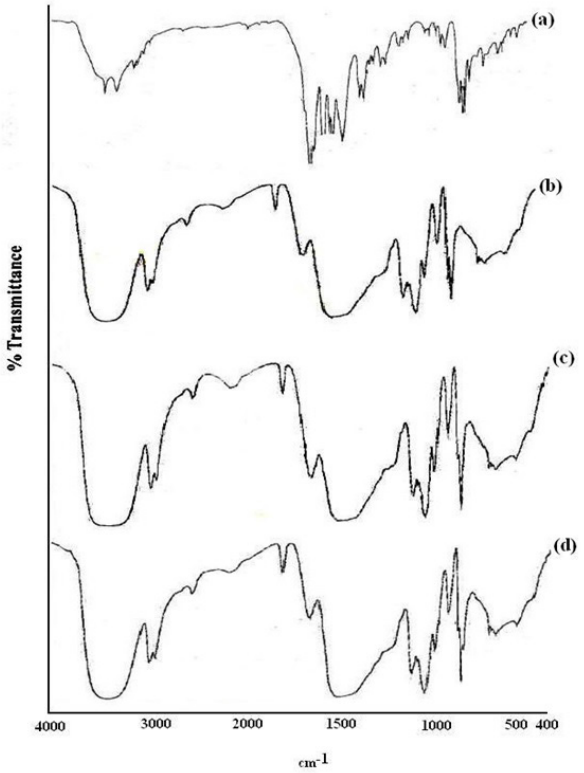

FIGURE 1 - FTIR spectra of pure diclofenac sodium (a) and dental pastes of diclofenac sodium (1 % w/w) prepared using MC (b), HEC (c) and NaCMC (d)

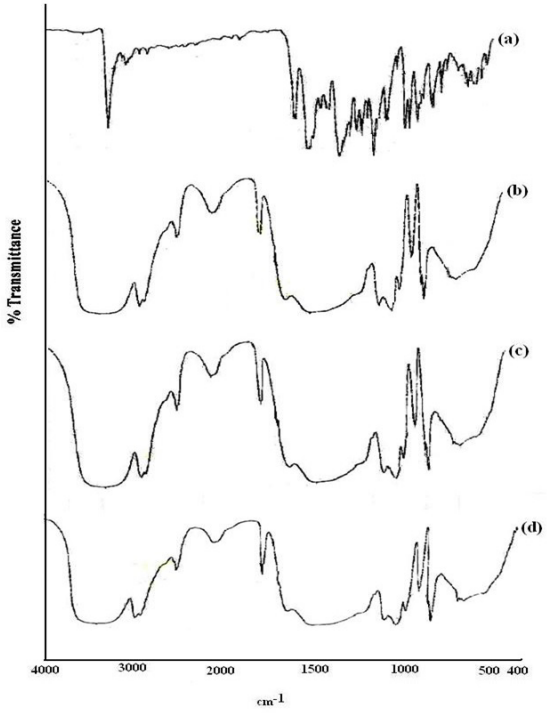

FIGURE 2 -FTIR spectra of pure nimesulide (a) and dental pastes of nimesulide (1 % w/w) prepared using MC (b), HEC (c) and NaCMC (d)

The *in vitro* drug release studies of diclofenac sodium and nimesulide (1 % w/w) dental pastes were carried out in 6.4 pH phosphate buffer solution and the drug release patterns are shown in Figure 3 and Figure 4. The increasing order of diclofenac sodium and nimesulide release rate from these dental pastes containing hydrocolloids was as follows: NaCMC < HEC < MC.

The data of *in vitro* release of diclofenac sodium and nimesulide from these formulated dental pastes were evaluated kinetically using various mathematical models: Zero-order model: $Q = kt + Q_0$; First-order model: $Q = Q_0 e^{k.t}$; Higuchi model: $Q = kt^{0.5}$; Korsmeyer-Peppas model: $Q = kt^n$; where Q = drug released amount in time t, Q_0 = start value of Q; k = rate constants and n = release exponent.Again, the Korsmeyer-Peppas model was employed in *in vitro* diclofenac sodium and nimesulide release behavior analysis of various dental pastes to find out *in vitro* drug release mechanisms: Fickian (non-steady) diffusion (when $n \leq 0.5$), non-Fickian or "anomalous" diffusion (when n = within 0.5 and 1) and case-II transport (zero-order) (when $n \geq 1$) (Ansari, Risheshwar, Ali, 2017; Saleem, Taher, 2008; Sant, Swati, 2011). The results of curve-fitting of the *in vitro* release of diclofenac sodium and nimesulide from formulated dental pastes into above mentioned mathematical models are presented in Table IV.

Ex vivo mucoadhesive evaluation of these diclofenac sodium and nimesulide (1 % w/w) dental pastes of was carried out using bovine check pouch. *Ex vivo* mucoadhesive strengths of diclofenac sodium (1 % w/w) dental pastes were measured within the range, 28.67 ± 0.20 to 165.13 ± 0.51 g (Table V). *Ex vivo* mucoadhesive strengths of various nimesulide (1 % w/w) dental pastes were measured within the range, 28.67 ± 0.20 to 165.13 ± 0.51 g (Table V).

For the stability study, selected dental pastes were packed in the collapsible tubes and stored at refrigeration (5°C ± 1°C) temperature for 1 h, 45°C ± 2°C, under 70 ± 5 % relative humidity (RH) for 4 weeks. The drug content, pH, tube spreadability and tube extrudability was determined for selected dental pastes for their stability. The results are depicted in Table VI.

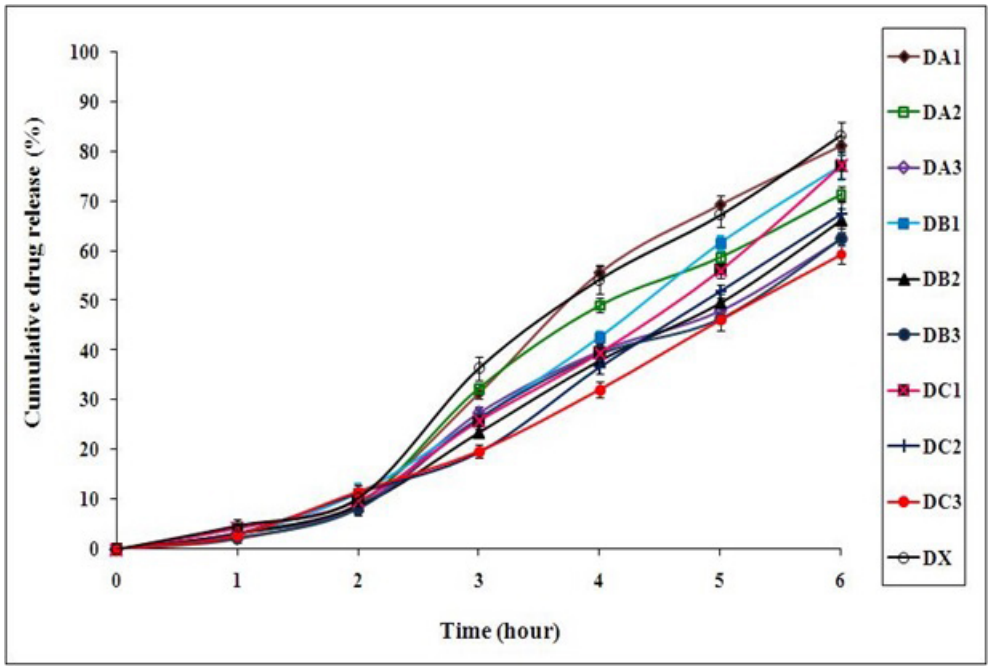

FIGURE 3 - In vitro diclofenac sodium release from dental pastes of diclofenac sodium (1 % w/w)

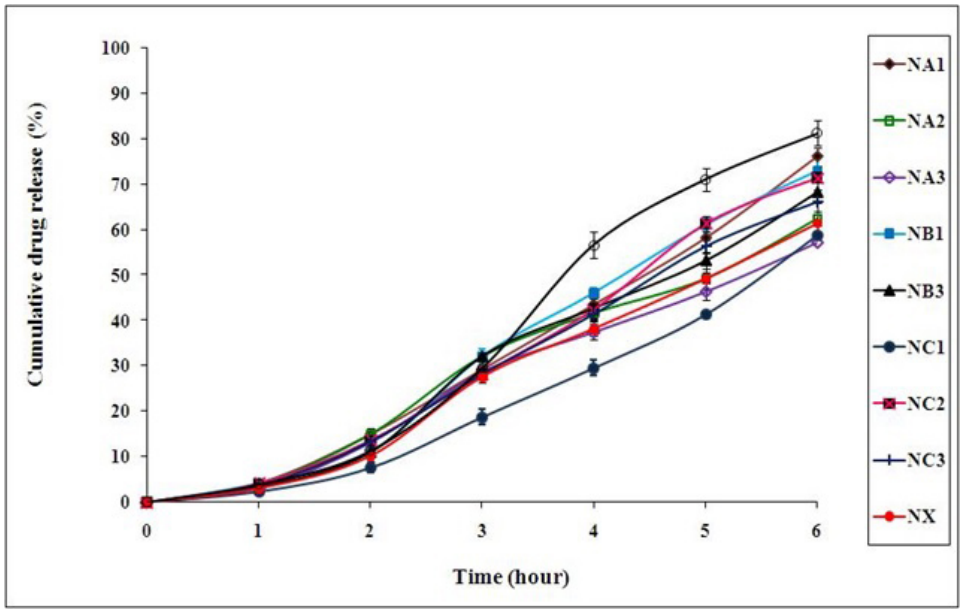

FIGURE 4 - In vitro nimesulide release from dental pastes of nimesulide (1 % w/w)

TABLE III - pH, drug content (%), viscosity (cps), tube spreadability and tube extrudability of various diclofenac sodium nimesulide (1 % w/w each) dental pastes

Formulation Code	pH	Drug Content (%)*	Viscosity (cps)	Tube Spreadability (cm)*	Tube Extrudability (%)*
DA1	6.06	99.63 ± 2.26	58756.91	7.12 ± 0.55	95.05 ± 2.37
DA2	5.96	98.62 ± 3.05	58967.84	7.43 ± 0.54	93.12 ± 3.72
DA3	6.13	99.51 ± 3.93	62340.87	7.72 ± 0.53	90.88 ± 2.28
DB1	6.16	96.75 ± 1.62	59862.92	7.16 ± 0.68	91.04 ± 2.74
DB2	5.96	97.14 ± 2.88	61672.57	7.26 ± 0.54	86.93 ± 1.52
DB3	5.90	96.43 ± 1.82	63706.95	7.45 ± 0.63	86.07 ± 2.86
DC1	5.93	98.10 ± 2.95	61261.67	6.10 ± 0.58	94.29 ± 3.92
DC2	5.86	98.07 ± 3.28	63307.91	6.47 ± 0.40	90.89 ± 3.69
DC3	6.26	96.89 ± 3.04	65259.92	6.63 ± 0.57	86.46 ± 1.86
DX	6.96	99.36 ± 3.52	40065.08	8.10 ± 0.65	96.39 ± 2.73
NA1	6.66	99.63 ± 3.74	58754.21	7.45 ± 0.26	96.27 ± 3.26
NA2	6.80	98.62 ± 3.27	58961.06	7.36 ± 0.49	93.94 ± 0.96
NA3	6.56	99.51 ± 3.06	63345.28	7.16 ± 0.34	90.95 ± 0.98
NB1	6.73	96.75 ± 2.30	59856.37	7.53 ± 0.26	93.27 ± 1.95
NB2	6.86	97.14 ± 1.28	61670.03	7.48 ± 0.20	91.37 ± 1.26
NB3	6.73	96.43 ± 1.74	63706.50	7.13 ± 0.33	88.94 ± 1.02

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Formulation Code	pH	Drug Content (%)*	Viscosity (cps)	Tube Spreadability (cm)*	Tube Extrudability (%)*
NC1	6.73	98.10 ± 3.19	61305.25	7.40 ± 0.48	89.85 ± 1.15
NC2	6.83	98.07 ± 3.28	63268.51	7.16 ± 0.36	86.23 ± 1.04
NC3	6.83	96.89 ± 2.27	65261.02	6.63 ± 0.44	83.48 ± 0.96
NX	6.66	99.36 ± 2.59	40056.25	8.02 ± 0.38	96.10 ± 2.36

*Mean ± SEM; n = 3

TABLE IV - Curve-fitting in vitro drug release data of various diclofenac sodium and nimesulide (1 % w/w each) dental pastes

Formulation Code	Correlation coefficient (R2)				Diffusional exponent (n)
	Zero-order model	First-order model	Higuchi model	Korsmeyer-Peppas model	
DA1	0.9801	0.8669	0.2944	0.9895	1.1143
DA2	0.9886	0.8710	0.2147	0.9912	1.1242
DA3	0.9858	0.8883	0.2785	0.9893	1.1437
DB1	0.9896	0.9055	0.2163	0.9862	1.1291
DB2	0.9874	0.9221	0.2530	0.9817	1.1502
DB3	0.9847	0.8721	0.2035	0.9896	1.2115
DC1	0.9781	0.9441	0.2609	0.9894	1.1323
DC2	0.9798	0.9297	0.2625	0.9975	1.1768
DC3	0.9878	0.9071	0.2438	0.9951	1.1653
DX	0.9329	0.9845	0.3697	0.9589	0.6643
NA1	0.9950	0.9004	0.3488	0.9953	1.0986
NA2	0.9888	0.8462	0.4355	0.9863	1.0999
NA3	0.9925	0.8370	0.3787	0.9832	1.0116
NB1	0.9897	0.8966	0.3066	0.9841	1.0169
NB2	0.9879	0.8720	0.3082	0.9804	1.0193
NB3	0.9767	0.9299	0.2204	0.9971	1.0194
NC1	0.9925	0.9034	0.3312	0.9956	1.0296
NC2	0.9961	0.8843	0.3506	0.9912	1.0203
NC3	0.9925	0.8792	0.3028	0.9851	1.0750
NX	0.9442	0.9893	0.3523	0.9574	0.6741

TABLE V - Mucoadhesive strengths (g) of various diclofenac sodium and nimesulide (1 % w/w each) dental pastes

Formulation code	Mucoadhesive strength (g)
DA1	58.95 ± 0.42
DA2	67.19 ± 0.10
DA3	73.34 ± 0.32
DB1	121.73 ± 0.39
DB2	127.72 ± 0.29
DB3	135.31 ± 0.11
DC1	151.84 ± 0.43
DC2	156.08 ± 0.54
DC3	165.13 ± 0.51
DX	28.67 ± 0.20
NA1	58.16 ± 0.03
NA2	67.06 ± 0.03
NA3	73.11 ± 0.06
NB1	119.16 ± 0.43
NB2	127.26 ± 0.33
NB3	134.53 ± 0.42
NC1	150.80 ± 0.39
NC2	156.15 ± 0.36
NC3	167.21 ± 0.18
NX	28.12 ± 0.02

*Mean ± SEM; n = 3

DISCUSSION

Dental pastes containing NSAIDs such as diclofenac sodium and nimesulide (1 % w/w) can be used for the effective management of dental pain and inflammation with local delivery into the periodontal pockets. The pH of dental pastes may change the oral environment, slightly acidic or basic pH may promote irritation of oral mucosa on application. Measured pH of the formulated dental pastes was within the acceptable limit as pH less than 4.5 will lead to enamel erosion (Table III) (Benjakul, Chuenarrom, 2011). This can produce oral mucosal irritation upon application. Formulated dental pastes exhibited uniform distribution of active ingredient. Moreover, the drug content was found to be in acceptable range (Table III). The viscosities of diclofenac sodium (1 % w/w) and nimesulide (1 % w/w) dental pastes were above 40000 cps (Table III).It was apparent that pastes without the presence of hydrocolloid polymers (DX and NX) exhibited low viscosity. It was further manifested that the paste exhibited higher viscosity as the concentration of hydrocolloid polymer was increased. Highest viscosity was endured by formulation DC3 and NC3 which contained 2.5% w/w of NaCMC. This may be attributed to ion binding and hydrogen bonding phenomenon of NaCMC (Shailaja *et al*., 2012).

In both dental pastes (DX and NX), the tube spreadability was found better, especially when pastes were prepared without the incorporation of hydrocolloid polymers. The tube spreadability of the formulated dental pastes decreased with an increase in hydrocolloid concentration. Spreadability plays an important role in patient compliance and help in uniform application of paste. A good paste takes less time to spread and will have high spreadability. The extrusion of paste from collapsible tube is important during application and for the patient compliance. Pastes with high viscosity may not extrude from the tube easily whereas low viscous pastes may flow quickly.

The FTIR results indicated absence of any drug-excipient incompatibility in the formulated dental pastes of diclofenac sodium and nimesulide (Figure 1 and 2).

The *in vitro* release of diclofenac sodium and nimesulide from all these dental pastes was found to be sustained over a long period of time (Figure 3 and Figure 4). The *in vitro* percent drug release from the formulated pastes decreased as the concentration of mucoadhesive polymer was increased in the formula. The decrease in *in vitro* release of diclofenac sodium and nimesulide from these dental pastes may be imputed to the increase in the viscosity of the pastes. The drug release from dental pastes containing MC was found lower as compared to dental pastes containing HEC and NaCMC.

When respective correlation coefficients were compared, it was found that the drug release for paste containing hydrocolloid polymer followed zero order release obeying Korsmeyer–Peppas model (n = 1).

The release exhibited case II transport mechanism (Table IV). However, dental pastes prepared without hydrocolloid polymers (DX and NX) followedfirst-order model. The result indicated that the *in vitro* release of diclofenac sodium and nimesulide from DX and NX dental pastes followed non-Fickian (anomalous) diffusion mechanism.

Ex vivo mucoadhesive evaluation of these dental pastes of was carried out using bovine check pouch. *ex vivo* mucoadhesive strength of these dental pastes containing hydrocolloid polymers followed: MC < HEC < NaCMC. The dental pastes prepared with 2.50 % of NaCMC (DC3 and NC3) displayed highest mucoadhesive strength (Table V). This mucoadhesive property may be beneficial to make intimate contact with the site of action (*i.e.*, mucus layer overlying the epithelial tissue). This may also be helpful to maintain consistent release of drugs over prolonged time at the site of application (Das, Nayak, Nanda, 2013; Malakar, Basu, Nayak, 2014).

Selected formulations were subjected for stability studies following the ICH guidelines. The stability study results reveal that the DC3 and NC3 dental paste formulations were found stable enough over a longer period in different storage conditions (Table VI).

TABLE VI - Stability results of diclofenac sodium and nimesulide (1 % w/w) dental paste formulation DC3

Storage Temp (ºC)	Time of Analysis	pH	Drug Content (%)*	Tube Spreadability (cm)*	Tube Extrudability (%)*
Diclofenac sodium (1% w/w) dental paste					
5°C ± 1°C	1 h	6.26	96.89 ± 3.04	6.62 ± 0.38	86.46 ± 1.86
45°C ± 2°C	1st week	6.26	96.68 ± 3.73	6.57 ± 0.35	86.02 ± 2.14
	2nd week	6.24	96.60 ± 3.82	6.57 ± 0.48	85.88 ± 2.07
	3rd week	6.25	96.47 ± 3.42	6.55 ± 0.44	85.66 ± 1.93
	4th week	6.24	96.05 ± 3.93	6.48 ± 0.52	84.44 ± 1.86
Nimesulide (1 % w/w) dental paste					
5°C ± 1°C	1 h	6.82	96.86 ± 2.17	6.60 ± 0.43	83.46 ± 1.86
45°C ± 2°C	1st week	6.76	96.73 ± 3.18	6.57 ± 0.35	83.02 ± 2.14
	2nd week	6.72	96.64 ± 3.02	6.57 ± 0.48	82.88 ± 2.07
	3rd week	6.66	96.54 ± 3.51	6.55 ± 0.44	82.63 ± 1.93
	4th week	6.57	96.33 ± 3.03	6.48 ± 0.52	82.46 ± 1.86

*[Mean ± SEM; n = 3]

CONCLUSION

The current study was undertaken to formulate and evaluate dental pastes containing NSAIDs, namely, diclofenac sodium and nimesulide (1 % w/w) to treat periodontitis. Dental pastes were prepared by conventional trituration method. Physicochemical evaluation studies, suggested optimum tube extrudability and tube spreadability characters. Drug content, pH and viscosity for all formulation was within the acceptable ranges. The *in vitro* drug release of formulated diclofenac sodium and nimesulide (1 % w/w) dental pastes carried out in 6.4 pH phosphate buffer solution displayed sustained release over longer period. The drug release followed the following order NaCMC < HEC < MC. The *in vitro* drug release from dental pastes prepared with hydrocolloid polymers followed zero-order kinetic model with case-II transport mechanism; whereas the *in vitro* drug release

from dental pastes prepared without the hydrocolloid polymers (DX and NX) followed first-order kinetic model obeying non-Fickian (anomalous) diffusion mechanism. FTIR results indicated no drug-excipient incompatibility. The formulated pastes displayed good adhesion to the oral mucosa revealing more retention time in mouth when tested for *ex vivo* mucoadhesion using bovine cheeck pouch. This can be beneficial to get intimate contact with the site of action during and after application to maintain consistent sustained release of drugs over prolonged time. The stability study results reveal that the DC3 and NC3 dental paste formulations were found stable enough over a longer period in different storage conditions.

REFERENCES

Ahmed MG, Harish NM, Charyulu RN, Prabhu P. Formulation of chitosan-based ciprofloxacin and diclofenac film for periodontitis therapy. Trop J Pharm Res. 2009;8(1):33-41.

Ali M, Singh S, Kumar A, Singh S, Ansari M, Pattnaik G. Preparation and in vitro evaluation of sustained release matrix tablets of phenytoin sodium using natural polymers. Int J Pharm Pharm Sci. 2010;2(3):174-79.

Ali MS, Ali J, Ahuja A, Alam MS. Formulation and characterization of dental film containing ofloxacin. J App Pharm Sci. 2012;2(11):114-9.

Amit N. Thermodynamic study of the diclofenac sodium solubility in various oils. Khimiya. 2010;19:121-8.

Ansari MT, Risheshwar P, Ali S. Effects of polymers on complexation efficiency of aceclofenac-beta cyclodextrin inclusion complex. Int J Pharm Bio Sci. 2017;8(4):21-9.

Barat R, Srinatha A, Pandit J, Anupurba S, Mittal N. Chitosan inserts for periodontitis: Influence of drug loading, plasticizer and crosslinking on in vitro metronidazole release. Acta Pharm. 2007;57(4):469-77.

Barat R, Srinatha A, Pandit JK, Ridhurkar D, Balasubramaniam J, Mittal N, Mishra DN. Niridazole biodegradable inserts for local long-term treatment of periodontitis: Possible new life for an orphan drug. Drug Delivery. 2006;13(5):365-73.

Benjakul P, Chuenarrom C. Association of dental enamel loss with the pH and titratable acidity of beverages. J Dental Sci. 2011;6(3):129-33.

Carvalho FC, Bruschi ML, Evangelista RC, Gremião MPD. Mucoadhesive drug delivery systems. Braz J Pharm Sci. 2010;46(1):1-17.

Das B, Nayak AK, Nanda U. Topical gels of lidocaine HCl using cashew gum and Carbopol 940: Preparation and in vitro skin permeation. Int J Biol Macromol. 2013;62:514-17.

Etienne D. Locally delivered antimicrobials for the treatment of chronic periodontitis. Oral Dis. 2003;9(s1):45-50.

Ferraz MP, Mateus AY, Sousa JC, Monteiro FJ. Nanohydroxyapatite microspheres as delivery system for antibiotics: Release kinetics, antimicrobial activity, and interaction with osteoblasts. J Biomed Mater Res Part A. 2007;81A(4):994-1004.

Jones DS, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. Int J Pharm. 1997;151(2):223-33.

Killoy WJ. Chemical treatment of periodontitis: local delivery of antimicrobials. Int Dental J. 1998;48(S3):305-15.

Lindhe J, Haffaiee AD, Socransky SS. Progression of periodontal disease in adult subjects in the absence of periodontal therapy. J Clin Periodont. 1983;10(4):433-42.

Malakar J, Basu A, Nayak A. Candesartan Cilexetil Microemulsions for Transdermal Delivery: Formulation, in-vitro Skin Permeation and Stability Assessment. Curr Drug Delivery. 2014;11(3):313-21.

Pataquiva Mateus AY, Ferraz MP, Monteiro FJ. Nano-hydoxyapatite microspheres for periodontitis treatment: Preparation and cytotoxicity studies. Eur Cells Mater. 2007;14:85.

Patel TK, Patel VM. Formulation and evaluation of medicated dental pastes for treatment of periodontitis. Int J Pharm Innov 2013;3(1):16-21.

Saleem MA, Taher M, Sanaullah S, Najmuddin M, Ali J, Humaira S, Roashan S. Formulation and evaluation of tramadol hydrochloride rectal suppositories. Indian J Pharm Sci. 2008;70(5):640-4.

Sant S, Swati S, Awadhesh K, Sajid M, Pattnaik G, Tahir M, Farheen S. Hydrophilic polymers as release modifiers for primaquine phosphate: Effect of polymeric dispersion. ARS Pharm. 2011;52(3):19-25.

Seymour RA, Heasman PA, Macgregor IDM. The pathogenesis of periodontal disease. In: Drugs, Disease and the Periodontium. Oxford: Oxford University Press. 1992. p.1-10.

Shailaja T, Latha K, Sasibhushan P, Alkabab AM, Uhumwangho MU. A novel bioadhesive polymer: grafting of tamarind seed polysaccharide and evaluation of its use in buccal delivery of metoprolol succinate. Der Pharm Lett. 2012;4:487-508.

Soskolone WA, Freidman M. Intra-periodontal pocket drug delivery. In: Rathbone MJ. edited. Oral Mucosal Delivery. Marcel Dekker, New york. 2004. p.359-79.

Williams RC, Jeffcoat MK, Howard HT, Rolla A, Stubbs D, Teoh KW, Reddy MS, Goldhaber P. Altering the Progression of Human Alveolar Bone Loss With the Non-Steroidal Anti-Inflammatory Drug Flurbiprofen. J Periodontol. 1989;60(9):485-90.

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