Development and Evaluation of Polymer Drug Delivery System (PDDS) for Delivery of *Boswellia seratta*

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Abstract: Boswellia seratta (BS) is the best herbal medicine to treat Rheumatoid Arthritis (RA), due to its anti-inflammatory and anti-arthritic activity. Delivering BS through an oral drug delivery system has been in effective, because of its enzymatic degradation within the Gastro-Intestinal (GI) tract. In this paper, we develop a gastro retentive approach for delivering BS to avoid high hepatic first pass metabolism and optimized buccal patch based on the drug delivery characteristics. There are seven different formulated buccal films of BS that were prepared by the solvent casting method, using mucoadhesive polymers, Poly Vinyl Alcohol (PVA), and Sodium Carboxy Methyl Cellulose (SCMC). These with drug formulation can be represented as PCB. The prepared films were evaluated by various physicochemical properties and characterization studies. Results obtained from physico-chemical properties, in-vitro and ex-vivo studies among all seven patches, PCB5 shows better drug-releasing characteristics. This was further confirmed by FT-IR and XRD characterization studies. Also, the data was statistically analysed using Analysis of Variance (ANOVA).

Keywords: Buccal films, Boswellia seratta, mucoadhesive polymers, Rheumatoid Arthritis (RA)

1.Introduction

In the current scenario, people suffer from joint diseases due to unpredictable weather, less physical activity, improper/unhealthy food habits, etc. But, these are the secondary reasons responsible for joint diseases. The primary reason is age. Although several types of joint diseases exist, a significant number of people are affected by Rheumatoid Arthritis (RA).RA is one of such chronic autoimmune diseases which causes the joints to swell, thus resulting in pain, stiffness, and progressive loss of function over time. In addition, people with RA also suffer from weight loss, low-grade fever, and fatigue.

RA often affects pairs of joints (both hands, both feet, etc.) and sometimes affects more than one joint; this includes the smaller joints in the wrists and hands. Over time, other joints such as shoulders, elbows, knees, feet, and ankles can be affected [1, 2]. Two conventional treatments available from the allopathic system come with side effects [3]. Hence a potential alternative solution is required for the delivery of drugs that face low bioavailability, harsh Gastrointestinal (GI) environment, and high hepatic first pass metabolism [4, 5].

The buccal drug delivery system is better when compared to various other available drug delivery systems, because of its salient features such as effectiveness, safety, and feasibility in administering drugs to patients. Some drugs are not suitable for oral administration because of metabolism happening in the GI tract. Moreover, the drugs which are delivered from the mucosal surface can easily get into the oral cavity and have the following distinct advantages (i) prevent first-pass metabolism [6, 7] (ii) improve bioavailability, and (iii) economic and patient-friendly [8]. Boswellia Seratta (BS) excels among herbal medicines for RA due to its anti-inflammatory and anti-arthritic activity [9, 10]. Based on different clinical evaluations, it has been proved that the H15 extract from Boswellia seratta resin is much suitable for curing RA [11]. But this herbal medicine may not be suitable for the oral drug delivery system because of its low bioavailability, enzymatic degradation within the GI tract [12], and high first-pass metabolism [13].

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Buccal films are the best alternatives and non-invasive routes to deliver herbal medicines, due to their bioavailability and for avoiding the presystemic elimination within the GI tract [14]. This can be governed by mucoadhesive polymers containing the drug. Mucoadhesive polymers are classified based on their (i) origin (natural or synthetic), (ii) chemical structure (cellulose or polyacrylates), and (iii) the binding mechanism of polymers on the mucosa surface. The vital role of the polymer mucoadhesion depends upon its surface charge, either positive (Cationic) (or) negative (Anionic), and its ionic interaction with the biological membrane. But in the case of non-ionic polymers, the mucoadhesion is examined by the chain entanglement of polymers [15].

The scope of the present work is to develop a novel buccal drug delivery system for Boswellia Seratta through a gastro retentive approach, by using mucoadhesive polymers. This approach offers more advantages when compared to other conventional drug delivery systems. In this work, gastro retentive formulation was developed by using buccal film formation with two mucoadhesive polymers, namely non-ionic polymer polyvinyl alcohol and ionic polymer SodiumCarboxyMethylCellulose (SCMC) to improve the bioavailability.

2.Materilas and methods

2.1. Materials

Boswellia Seratta (BS) Medical grade, procured from AGHP enterprises, Chennai. Polyvinyl alcohol (PVA) (Fisher Scientific) with 35-50cp viscosity and degree of hydrolysis 85-89%. Sodium Carboxy methylcellulose (SCMC) with medium viscosity was obtained from Sigma-Aldrich, Phosphate buffered saline (PBS) pH 6.8, and other chemicals were purchased and used in this fabrication process, were of analytical grade.

2.2. Boswellia extract and Buccal film preparation method

Boswellia Seratta (BS) was procured in the form of lumps. These lumps were crushed well and sieved using 250μm mesh.1% drug extract was prepared using 0.5g sieved particles dissolved in 100mL ethanol and filtered; this filtrate was used as the drug throughout the studies conducted for this research.

Table 1. Formulation of Mucoadhesive Buccal film (PVA/SCMC) with Boswellia Seratta

Formulation Code	PVA (w/v) %	SCMC (w/v) %	BS (mg)	plasticizer Glycerol (mL)
PCB1	5	0	500	1
PCB2	3.5	1.5	500	1
PCB3	3	2	500	1
PCB4	2.5	2.5	500	1
PCB5	2	3	500	1
PCB6	1.5	3.5	500	1
PCB7	0	5	500	1

2.3. Preparation of Buccal film

Seven different polymer compositions based on PVA/SCMC buccal film were prepared by the solvent casting method. The mass volume concentration of polymers Boswellia Seratta (BS) drug and Plasticizers were mentioned in (Table 1). The concentration of a drug and Glycerol plasticizer are maintained as constant for all formulations of the film. Based on their formulation, different proportions of ionic and non-ionic polymers were accurately weighed, separately dissolved in distilled water, and allowed to be stirred for 24 h at 300 rpm using a magnetic stirrer. Then these two polymer solutions were added into the drug solution mixture and then stirred at 500 rpm until a homogenous clear solution was obtained. The resultant solution was then poured into a 50 mm diameter petri dish and kept in the

oven at 40ºC, for drying. After 24 h drying, the dried buccal films were removed from petri dish and stored in a desiccator for further studies.

2.4. Physico-chemical properties

The appearance of the films was macroscopically evaluated. The films should have a smooth, soft, transparent appearance without a bubble.

2.5. Thickness study

The thickness of three film samples from each formulation were measured using a thickness gauge micrometer (Mitutoyo, Japan) at three different positions and their average values was determined [5, 7].

2.6 Weight of the film

In each formulation, three samples of size ($2x2cm^2$) films were weighed individually by using a digital balance and mean weight was calculated and reported as weight of the film and its unit is given as mg [16,17].

2.7. Folding endurance

In each formulation, the folding endurance of three films of same dimensions was determined, by the film being repeatedly folded at the same place without rupturing. The mean value of each formulation strip was calculated to determine the value of folding endurance [6].

2.8 Swelling index

The degree of swelling of three sample of dimension ($2x2cm^2$) from each formulation were initially weighed (W_1) and immersed into a separate Petri dish, which contains 3mL of simulated saliva medium with pH 6.8. This medium was made of Phosphate Buffer Solution (PBS) with pH 6.8 and left for an hour [16]. After which, the swollen film was taken out from the Petri dish to wipe excess solvent by using tissue paper and carefully reweighed (denoted as W_2). The swelling index was calculated using the following formula

$$SI (\%) = (W_2-W_1)/W_1 \times 100$$

SI=Swelling Index (%), W1=Initial Weight of film, W2=Weight of swollen film

2.9 Surface pH of the buccal film

Three Buccal patches from each seven formulations were allowed to swell for an hour over the surface of the agar plate to determine the surface pH, by using pH indicating paper which was prepared by 2% (w/v) agar in warmed simulated saliva fluid with pH 6.8. Continuous stirring takes place until a homogeneous solution is obtained which was then poured into a Petri dish and allowed to form the gel at room temperature [18].

2.10. Drug content

Three film sample of dimension ($2x2cm^2$) from each formulation were taken and being solvated in 100mL phosphate buffer solution (pH 6.8), stirred for 2 h, and then the solution was filtered. 5mL of the solution was drawn out from the filtered solution and diluted with pH 6.8 buffer solution up to 20mL. Absorbance was measured for resulting solution by using UV spectrometer (Varian model no 4000) at 242nm [7]. From the calibration curve the drug content (%) was calculated based on the following formula [35, 36].

Drug content = (Absorbance /slope) X dose X dilution factor X (1/1000)
% Drug Content = (Drug content/Dose of formulation) X 100

2.11. In vitro-drug release studies

In the vitro-drug release studies were carried out for three film sample of dimension ($2\times2 cm^2$) of each formulation. The one side of the buccal film sample were fixed and attached to a separate beaker containing 100 mL Phosphate buffer solution (pH6.8). This dissolution process was carried out in a modified dissolution apparatus at room temperature, stirred at 150 rpm. After a predetermined interval, 3mL of the solution was withdrawn from the solution and immediately replaced with the same volume of fresh PBS (pH 6.8) without any change in the quantity of solution. For every 15 min, samples were taken out and analyzed for the drug content by UV spectrometer (Varian model no4000) at 242 nm [19]. The cumulative drug release was calculated using the following formula [32]

$$\text{Cumulative percentage release } (\%) =$$
$$= (\text{Volume of sample withdrawn (mL)/bath volume (v)}) \times P(t-1) + Pt$$

where Pt = Percentage release at time t
P (t - 1) = Percentage release previous to 't'

2.12. Muco adhesion strength

Mucoadhesion strength of buccal film from each formulation was examined by a modified physical balance method as described by Gupta et.al [31] for which, the goat intestinal mucosa acts as the mucosa membrane. The test method was conducted within three hours after the procurement of goat intestinal mucosa from the local slaughterhouse. Initially, the mucosa membrane was cleaned well with saline water and then stuck over the glass slab with the help of cyanoacrylate adhesive. Glass slab was vertically placed in a 250 mL empty beaker. Three films from each formulation were taken and one surface of each film was hydrated with PBS (pH 6.8). The hydrated film surface was brought up to be in contact with the mucosa membrane. Then the water was slowly added to the 250mL beaker until film detachment occurred from the mucosa membrane. The mucoadhesion strength of the film was measured based on the amount of water present in the beaker [5]. After completing the experiment, the mucoadhesive strength was calculated based on the following formula:

Mucoadhesive Strength (g) = (Weight of beaker +Weight of water) - Weight of empty beaker.

2.13. Ex -vivo Permeation studies

The ex-vivo permeation study was carried out in a Modified Franz diffusion cell which has two compartments such as the Receptor and Donor. This experiment begins with the Receptor compartment which was filled with 100mL PBS (pH 6.8) and a cleaned, fresh goat mucosa was placed between the Receptor and Donor compartments. The buccal film ($2\times2 cm^2$) was cut from each formulated batch and placed over the mucosa membrane. The donor compartment was fixed over it. The whole experiment setup was placed over the magnetic stirrer. The content present in the Receptor compartment was continuously stirred and the temperature was maintained at room temperature. After a predetermined period (every 30 min), the samples were drawn out from the Receptor compartment and analyzed by a UV spectrometer at 242nm [15].

2.14 Statistical analysis

The data of seven different buccal film formulations and their drug-releasing profile were theoretically analysed using a one-way analysis of variance (ANOVA) evaluated for statistical significance (p-value < 0.05). The data of each formulation were compared using Least Square Mean values [20].

2.15. Fourier Infra-Red spectroscopy (FT-IR)

The chemical interaction between polymer and drug was examined by Bruker FTIR in the wavelength ranging from 4000cm^{-1} to 500cm^{-1} [21-25].

2.16. X-Ray dffraction studies

Wide Angle XRD patterns of selected mucoadhesive film and pure polymers (PVA and SCMC) were determined by the Sixth generation XRD diffractometer (model Rigaku Miniflex -II) build up with copper source radiation. The 2θ values were recorded in the scanning range of 10^0 to 70^0 [26].

3. Results and discussions
3.1. Physicochemical properties

Table 2. Physicochemical properties of the buccal film

Formulation code	Thickness (mm)	Flatness (%)	Film weight (mg)	Drug content (%)	Folding endurance (timings)	Swelling Index (%)	Surface Ph	Muco-adhesion strength, (g)
PCB 1	0.8	98.0	0.06	98	260	280	6.5	15.42
PCB 2	0.6	98.8	0.04	97	280	320	6.4	16.12
PCB 3	0.4	97.4	0.02	98	293	396	6.7	19.21
PCB 4	0.5	97.3	0.11	99	312	574	6.8	21.45
PCB 5	0.4	97.0	0.08	98	330	620	6.4	25.30
PCB 6	0.3	96.2	0.11	98	342	690	6.3	28.40
PCB 7	0.2	95.5	0.11	99	354	720	6.5	31.20

The physicochemical properties of the buccal film from each formulation are summarised in Table 2. Appearances of the films were found satisfactory in homogeneous, transparent, flexible, and soft texture without any imperfections due to the addition of enhancers [27]. The weights of the films were found in the range of 0.2-0.11 mg. This variation in films is due to a change of viscosity of the materials (PVA/SCMC) in different formulations. The flatness of the films is examined in the ranges from 95% to 98% as the length of the film is highly affected by the shrinkage characteristics of the SCMC material.

3.2. Drug content

Drug content and their dispersion is a very important aspect of the buccal film that has to be examined. Without this, each formulation can have different drug content. As mentioned in Table 2, it is evident that the major number of buccal film formulations in the present work was not less than 97%. Mostly, if the drug content is below 90%, it is not acceptable due to the heterogeneity between drug and polymer. So PCB1, PCB5, PCB6, and PCB7 buccal batches have optimum drug content [28].

3.3. Folding endurance

The flexibility of the film is more important for the buccal drug delivery system which was enhanced by the plasticizer. It is evident from the results that are obtained from the folding endurance test method. It shows that the flexibility of the film gradually increases in the range of 260-350 timings by the effect of the SCMC and additional volume of plasticizer content. Both factors have a positive response over film flexibility [16, 21].

3.4. Swelling index

The rate of swelling is an important factor because it can influence the bio adhesion characteristics of the film [5]. The rate of hydration for different formulations of the present study was in the order of PCB1<PCB5<PCB7. The degree of swelling depends on the type of polymer, concentration, and structure. Gel layer is formed depends upon the various concentration of SCMC and PVA materials.

Because of this gel layer formation the diffusion length of drug is increases [33] as per the results shown in Table 2, 'PCB7 formulation' which contains a high concentration of SCMC when compared to other formulations, had the highest swelling characteristics. The swelling character for PCB5 remained optimal.

3.5 Surface *p*H of the buccal film

To achieve patient compliance, the surface *p*H of a buccal film should be neutral; otherwise, it irritates the mucosa [25]. The surface *p*H of all formulations of seven batches was found to be in the range of 6.5 to 6.8. Hence, all formulations of seven batches were satisfactory and did not affect the mucosa membrane.

3.6. Mucoadhesion strength

The mucoadhesive strength of buccal film depends upon various combinations of mucoadhesive polymers, functional groups, and structure. In this study, the mucoadhesive strength of a polymer is determined by the entanglement of the polymer blend functional group and mucous proteins. It was concluded that the non-ionic polymer concentration greatly influences the mucoadhesive bonding between the polymer and mucosal surface. As a result, the PCB1 had much lower mucoadhesive properties when compared with other formulations because of the high amount of non-ionic content present in the PCB1 formulation. Whereas PCB5, PCB6, and PCB7 possess a high mucoadhesive property which may be due to the concentration of ionic polymer content (SCMC) present in that formulation to facilitate the controlled release of drug and improve patient compliance [5].
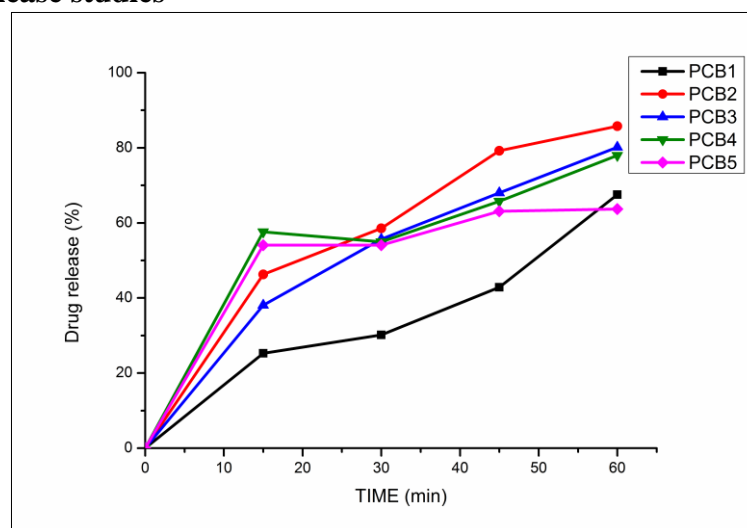
3.7. In-vitro drug release studies

Figure 1. The drug release profile of PVA and
SCMC and their combination along with drug

Figure 1 shows the drug-releasing profile of five combinations of PVA/SCMC buccal films with the drug. The drug was rapidly released from the buccal film for the first 15 min. After 15 to 60 min, the drug-releasing profile of each formulation slightly varied with each other due to their combination of polymers (PVA and SCMC). Most of the reports revealed that many numbers of hydroxyl groups present in the SCMC material lead to ready erosion and allow drug diffusion at a faster rate when compared with PVA [27]. In this study, the trend of the drug-releasing profile after 60 min was found to be PCB1< PCB2<PCB3<PCB4<PCB5, respectively. The first three formulations possessed a slow release of the drug due to the high percentage of PVA content and their molecules packing in this polymer chain. It was also concluded that formulation PCB5 had a moderate and promising drug release profile. Moreover,

it neither shows a burst release nor a very slow release. This phenomenon may be associated with the amount of PVA and SCMC.

3.8. Ex - vivo permeation studies

Figure 2 shows that the ex-vivo permeation studies of five different formulations of buccal film from PCB1 to PCB5 were performed using goat's oral mucosa since it resembles the oral mucosa of a human [28]. This drug permeation study revealed that the first three formulations released the drug from mucosa at a lower level rate when compared with the other four formulations due to their microstructural design.
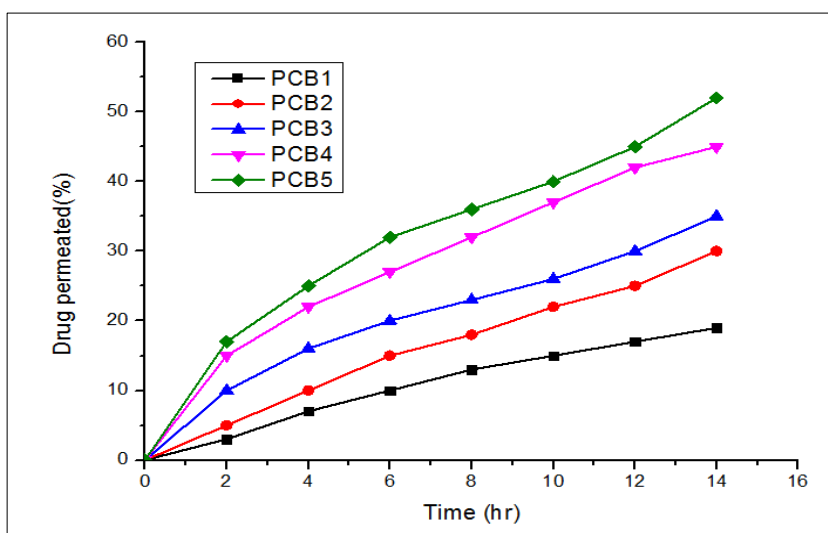

Figure 2. The Ex-vivo permeation profile of PVA and SCMC along with drug
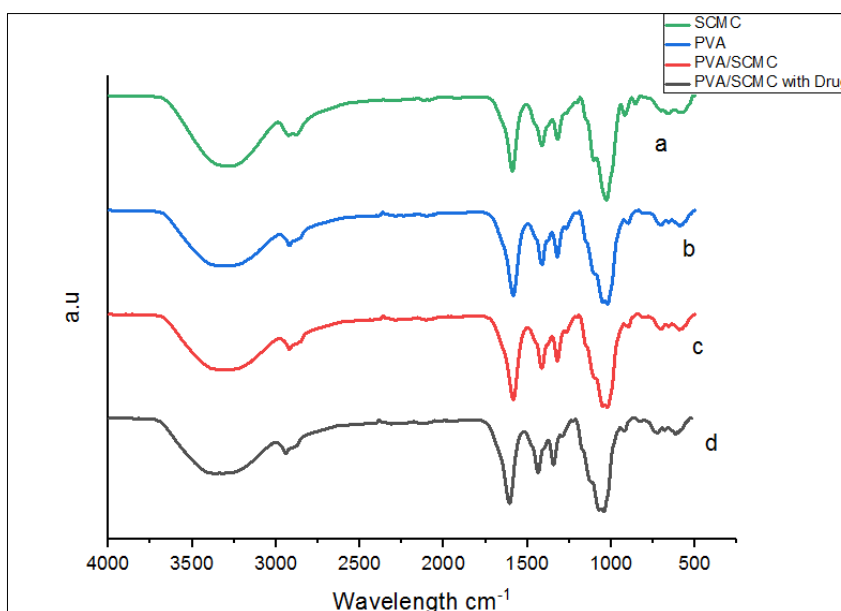
3.9. Drug - excipient interaction studies

Figure 3. A spectrum of Pure PVA and SCMC and their combination along with drugs

Figure 3 shows FTIR characterization spectra of pure polymer (a, b), combination of polymers (c), and polymers with the drug (d), observed over the frequency range 4000 cm^{-1}to 500cm^{-1}. From the spectrum of (a, b), pure polymer PVA and SCMC revealed a characteristic broad range peak at around 3457 cm^{-1}- 3000 cm^{-1}. It is representative of -OH stretching vibration due to inter and intramolecular

hydrogen bond [26] and the principal absorption band of both polymers (a, b) at 2937cm^{-1} attributed to -CH stretching due to bending of CH$_2$ groups. The absorption band around 1900cm^{-1} to 500cm^{-1} corresponds to the stretching of C=O and C-O from the rest of the acetate groups of PVA material. In the FTIR spectra of SCMC, the typical absorption band at 1584.7cm^{-1} due to the -COO stretching and the bands at around 1413cm^{-1}, 1321cm^{-1}, and 1050cm^{-1} attributed to -CH$_2$ scissoring, -OH bending vibration, and C-O stretching, respectively [27].

From these FTIR spectrum results, it is evident that there is no chemical bonding formation between the polymers and excipients.
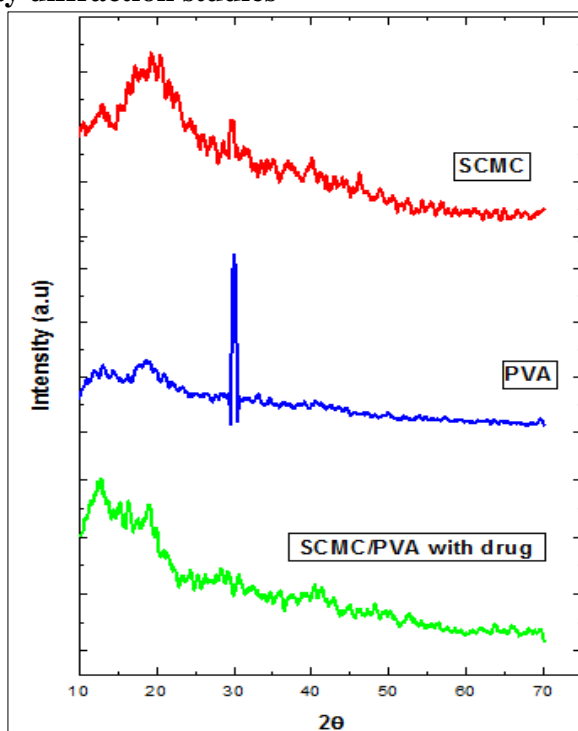
3.10. X-Ray diffraction studies

Figure 4. Diffractrograms of (a) Pure SCMC (b) Pure PVA (c) PVA/SCMC with Drug

The crystallographic structure of pure polymers (PVA and SCMC) and their selected combination with the drug (PCB5) are shown in Figure 4. The broad range peak of pure SCMC material was observed at 2Θ= 19.6º [29], which indicates the amorphous phase of SCMC [30]. On the other hand, a pure crystallographic structure of PVA is shown in Figure 4 at 2Θ = 10.8º, 19.8º, and 41.0º [30]. Figure 4 (c) SCMC/PVA/Drug shows that the absence of crystalline peaks confirms the drug thoroughly dispersed over the polymer matrix [29-31]

3.11. Statistical analysis

The swelling index, in-vitro release, and ex -vivo permeation studies revealed that the PCB5 formulation has a moderate drug-releasing profile. The ANOVA results show that PCB5 has highly significant p-values when compared to other PCB formulations at all time points except when compared to PCB7 at time point 30, where it is not significant.

4. Conclusions

The PVA/SCMC mucoadhesive buccal films loaded with drug Boswellia Seratta for rheumatoid arthritis have been prepared effectively. From the swelling studies, in-vitro and ex-vivo analysis, PCB5 formulation shows good drug delivery characteristics among the seven formulations. Hence the non-ionic (PVA) and ionic (SCMC) combination along with Boswellia seratta is a promising mucoadhesive buccal patch for rheumatoid arthritis.

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