

## Research Article

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## Novel, bucco-compatible simvastatin buccal film: An integrative study of the effect of formulation variables

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### Abstract

Present investigation was aimed to develop a novel bucco-compatible buccal film of simvastatin and to examine effect of formulation variables on physico-mechanical as well as drug permeation characteristics. Nine batches of films (BF1-BF9) were prepared by solvent casting method. Effects of plasticizers (glycerol, propylene glycol), penetration enhancers (dimethyl sulfoxide, eucalyptol oil) and polymers (HPMC, Carbopol) on drug permeation, long term stability and physico-mechanical parameters namely pH, folding resilience, mucoadhesive strength, swelling, in vitro residence time were investigated. Film's compatibility with buccal micro-flora was examined. Carbopol influenced the mucoadhesive and hydration properties, HPMC contributed towards film formation and drug release. Propylene glycol was promising than glycerol in imparting flexibility to films. Penetration enhancers facilitated drug permeation and dimethyl sulfoxide was found superlative than eucalyptol oil. SEM analysis confirmed uniform surface of films. Stability studies up to 6 months exhibited no substantial changes in buccal films. Films did not exhibit any inhibitory action against pro-biotic bacteria. The developed films were found to be bucco-compatible and formulation variables were observed to influence physico-mechanical as well as drug permeation characteristics of film.

**Keywords:** Buccal film, Bucco-compatibility, Carbopol, HPMC, Plasticizer, Penetration enhancer.

### Introduction

To search for better alternatives is an inherent penchant of human beings and this has been the reason for incessant growth in all spheres of life. As exquisiteness of science is to be discovered part by part, researchers cultivating drug delivery have witnessed a progressive growth since last few decades. Novel drug delivery systems such as phytosomes, liposomes, micro-/ nano-particles, and sustained/controlled release formulations were thought to have only academics or theoretical significance, but these are now ready to serve patients on the way to better quality of life.<sup>1-4</sup> Many novel techniques such as solid dispersion, self-emulsifying, gastro-retentive, muco-adhesive as well as targeted delivery are explored for increased efficacy of existing drugs.<sup>5-7</sup> Drug delivery through the transdermal or buccal route have been worked out extensively as novel drug delivery.<sup>8, 9</sup> Buccal drug delivery is one among the novel drug delivery systems which has attracted the responsiveness of formulation/drug delivery scientists over the globe. It is evident from the heavy volume of research publications in various international and national journals, that buccal drug delivery will be one of the most promising therapeutic arsenals in future time to come.<sup>10, 11</sup>

Many drug molecules have been reported to show better therapeutic effect via buccal route owing to its high vascular architecture. Safety and clinical examination in human volunteers have also been successful in delivering drugs through buccal route.<sup>12, 13</sup>

Buccal films and patches are of considerable interest to researchers as they qualify major prerequisite of a feasible and acceptable dosage form.<sup>14</sup> These are clinically proven to be effective but still could not reach market as a successful dosage form. Reasons for such status-quo might be the scale up problems of films/patches at industrial measure. In this regard, effect of different formulation and process variables play a very significant role. Another key part of buccal formulation is its compatibility and tolerability with buccal mucosa, which still remains as a derelict segment in buccal drug delivery. The effect of the drugs as well as excipients on the buccal micro-flora must be examined as an essential part of formulation development. Keeping the above facts into consideration, present investigation was carried out to study the effect of different formulation variables on performance of buccal films and to examine the compatibility with buccal micro-flora. Based on literature and our prior knowledge, we have identified plasticizers (glycerol, propylene glycol), penetration enhancers (dimethyl sulfoxide, eucalyptol oil) as well as polymers (HPMC, Carbopol) as paramount formulation variables and examined their effect on the physico-mechanical along with drug release/permeation behavior of buccal film. Simvastatin was chosen as a model drug as it exhibits suitable properties to be delivered by buccal route.<sup>15</sup>

Novelty of this work is to highlight the new-fangled aspects in buccal formulation to consider the tolerability and compatibility issues as well as to discuss the effect of formulation variables that affect performance of buccal film. The findings of the present investigation would emphasize some of the crucial issues associated in the development of film/patch formulations.

## **Materials and Methods**

Simvastatin was obtained as a gift samples from Ranbaxy Laboratories Ltd., India. Hydroxy propyl methyl cellulose (HPMC 50 cps), Carbopol 940, glycerol, propylene glycol and dimethyl sulfoxide were purchased from SD Fine chem. Ltd., India. Eucalyptol oil was procured from Sigma-Aldrich, Mumbai, India. Disposable Petri dish, nutrient agar, sodium chloride were procured from HiMedia Laboratories, Mumbai, India. All excipients,

chemicals and solvents were of analytical grade and used as received without any further modification. Fresh goat buccal mucosa was obtained from local slaughter house for ex vivo studies. Triple distilled water was used throughout the study.

## **Formulation of buccal film**

Buccal films were prepared by the solvent casting method with slight modification.<sup>16</sup> The composition of film formulation is shown in Table 1. Briefly, HPMC 50 cps and Carbopol 940 were prepared as 1% dispersion by stirring. Drug was dissolved in 3:2 ratios of acetone and isopropanol. Required quantity of polymer dispersion was added to the drug solution and stirred by magnetic stirrer. Plasticizers and penetration enhancers were added at last in the specified quantity. Lastly the above mixture was stirred for 1 h and then poured on glass Petri dish. After 24 h, the completely dried films were removed carefully, cut into one cm<sup>2</sup> size, wrapped in aluminum foil and stored for further studies. Placebo films were also formulated by following the same procedure.

## **Characterization of films**

Formulated buccal films were evaluated for different physico-mechanical parameters namely, pH, folding resilience, drug content, mucoadhesive strength, swelling index and in vitro residence time. Selected films were subjected to release/permeation studies to evaluate the effect of these formulation variables on drug release/permeation pattern. For characterization of films, samples were withdrawn randomly from each batch and all experiments were repeated thrice (n=3). Values of experimental results are expressed as mean  $\pm$  SD.

## **Surface pH**

An unused Petri dish was filled with 5 mL distilled water and buccal film was placed at the middle part of the Petri dish. After 1 h, the electrode of pH meter (Mettler Toledo AG) was touched to the surface of buccal and pH was measured.<sup>10</sup>

## **Folding resilience**

Folding resilience of the film was determined by a single person (research scholar) in order to avoid handling error (human error). Film was repeatedly folded at the same place till it broke. Number of times, the film could be folded at the same place (without breaking) was considered as the folding resilience.<sup>17</sup>

### Mucoadhesive strength

Mucoadhesive strength of the films was measured using previously reported modified 2-arm physical balance with slight modification.<sup>14, 18</sup> Briefly, on the left side pan a beaker was placed, right side pan was removed and fitted with a stainless steel ring fixed with a glass slide. Buccal film was fixed to the glass slide with adhesive. Fresh goat buccal mucosa was fixed to another stainless still dish with adhesive and then placed in a Petri dish containing phosphate buffer (pH 6.5). The film and the buccal mucosa were brought into contact and a preload of 50 g was placed for 5 min. Thereafter, preload was removed and water was then added into the beaker on the left side pan from a burette at a constant rate of  $100 \pm 5$  drops per minute. The weight of water required to detach film from the mucosa was noted as mucoadhesive strength.

### Swelling index

Selected film was weighed ( $W_1$ ) before subjecting to swelling study. Film was placed in a Petri dish containing 5 mL of phosphate buffer (pH 6.5) and allowed to swell. After 0.5, 1.0, 2.0 and 4.0 h time intervals, film was removed carefully and weighed ( $W_2$ ). Following formula was used to calculate swelling index.<sup>19</sup>

$$\text{Swelling Index (\%)} = \frac{[W_2 - W_1]}{W_1} \times 100$$

Where,  $W_1$  is the initial weight and  $W_2$  is the weight of swelled film

### Drug content

Selected film was cut into very small pieces and dissolved in 100 mL 0.01 M sodium buffer with 0.5% sodium dodecyl sulfate solution. The solution was filtered through 0.45  $\mu\text{m}$  filter. From the above stock solution, 10  $\mu\text{g/mL}$  concentration samples was prepared and scanned at 238 nm ( $\lambda_{\text{max}}$ ) by UV-VIS spectrophotometer (ELICO SL 164). Drug content was determined from the measured absorbance value. Solution of placebo was taken as the blank control.<sup>20</sup>

### In vitro residence time

Modified USP disintegration apparatus was used for the in vitro residence studies as previously reported.<sup>12, 21</sup> Goat buccal mucosa was glued to glass slide, attached to glass slab which was vertically connected to apparatus. The film was fixed into the mucosal membrane after slight hydration. The glass slab was moved up and down with a

constant speed. Time necessary for complete erosion or detachment of the film from the mucosa surface was recorded.

### Surface morphology

Surface morphology of some selected films were examined by SEM.<sup>22</sup> Films were coated with gold palladium with the help of a gold sputter module in a high vacuum evaporator after fixing on the stubs. Prepared samples were analyzed with LEO 420 (LEO Electron Microscopy Ltd., England) using secondary electron imaging. Good quality photographs of different views were captured and recorded for interpretation.

### In vitro drug release

Paddle over disc (65 mm) dissolution apparatus (USP 5, Electrolab India Pvt. Ltd.) was used for in vitro drug release study.<sup>23</sup> Film was placed at the bottom of the dissolution jar and disc was kept over it. Phosphate buffer of pH 6.8 (200 mL) was taken as dissolution media. Dissolution test was carried out at  $37 \pm 2^\circ\text{C}$  with  $50 \pm 2$  rpm speed and aliquots of 2 mL were withdrawn at pre-specified time intervals for 12 h, filtered through 0.45  $\mu\text{m}$  filter and equal volume of fresh pre-warmed phosphate buffer was added to maintain sink condition. The absorbance of aliquots was taken at 238 nm by UV-VIS spectrophotometer and quantity of drug released to the dissolution medium was calculated.

### Ex vivo drug permeation

Ex vivo drug permeation study was carried out by using Keshary-Chien diffusion apparatus.<sup>24</sup> Goat buccal mucosa (2.25  $\text{cm}^2$ ) was mounted on a diffusion cell between the donor and receptor compartment. The buccal film was fixed on the buccal mucosa. Phosphate buffer of pH 6.5 (5 mL) in the donor compartment and the phosphate buffer of pH 7.4 (45 mL) in the receptor compartment was filled. The fluid was maintained at  $37 \pm 2^\circ\text{C}$  and stirred continuously at  $50 \pm 2$  rpm. Aliquots of 1 mL were collected at predetermined intervals for 12 h, filtered through 0.45  $\mu\text{m}$  filter and the amount of drug was determined by measuring the absorbance of the aliquots at 238 nm using UV-VIS spectrophotometer. Freshly prepared, pre-warmed phosphate buffer was added to maintain sink condition.

### Bucco-compatibility evaluation

Growth inhibitory effect of films on pro-biotic microorganisms present in buccal micro-flora was

investigated by agar diffusion method.<sup>25</sup> Suspensions of the pro-biotic bacteria (*Lactobacillus acidophilus*, *Bifidobacterium infantis* and *Lactobacillus rhamnosus*) were spread on the agar plates containing media. Sterile paper discs of 5 mm diameter (Whatman cellulose filter papers) were put at the center of the seeded plates and 10 µL of film suspension (both drug loaded and placebo film) was applied to the disc. Plates were incubated at 37 °C for 36 h under an anaerobic atmosphere and the diameter of the growth inhibition zone were measured.

**Stability studies**

Film formulations (BF9) were subjected to stability analysis. These films were wrapped in aluminum foil and kept in an air tight glass container at 4 ± 0.5 and 22 ± 1°C for 6 months. Periodically (1, 3 and 6 month), these films were evaluated for all characterization parameters including surface morphology and in vitro drug release study.

**Results and Discussion**

Buccal films containing simvastatin were formulated in three different series namely, Series1, 2, and 3 (Table 1). Nine batches of films were formulated (3 batches in each

series) which differ from each other both qualitatively and quantitatively in the ratio of formulation variables. First series consisted of film formulations BF1, BF2 and BF3 containing HPMC and Carbopol in equal ratio (1:1), whereas the ratio of other variables was varied in previous order. Films in second series BF4, BF5 and BF6 were having 1:2 ratio of polymers (HPMC: Carbopol) and other variables were incorporated in previously order. In the last third series (BF7, BF8 and BF9) HPMC and Carbopol were in 2:1 ratio and other variables were same as previous series. Varying the formulation variables in random fashion facilitates to get a wide variety of films with different characteristics. Purposefully, this study was premeditated in such a manner that, we could be able to know the effect of polymers, plasticizer and penetration enhancers on the performance of buccal films in term of physico-mechanical as well as drug release/ permeation features. In the subsequent part, the results and discussion are presented in three different sections. In the first section, physico-mechanical parameters and formulation variables of films are discussed, in the second section, drug release/permeation aspects are conversed whereas in the last section the bucco-compatibility of developed films is discussed.

Table 1: Formulation variables of buccal films containing simvastatin

| Formulation series | Code/<br>Ingredients | Polymers (%)   |                 | Penetration enhancer (%) |                   | Plasticizer (%)     |          | Solvent                          |
|--------------------|----------------------|----------------|-----------------|--------------------------|-------------------|---------------------|----------|----------------------------------|
|                    |                      | HPMC<br>50 cps | Carbopol<br>940 | DMSO                     | Eucalyptol<br>oil | Propylene<br>Glycol | Glycerol |                                  |
| Series 1           | BF1                  | 1              | 1               | 0.25                     | 0.75              | 0.25                | 0.75     | Acetone:<br>Isopropanol<br>(3:2) |
|                    | BF2                  | 1              | 1               | 0.50                     | 0.50              | 0.50                | 0.50     |                                  |
|                    | BF3                  | 1              | 1               | 0.75                     | 0.25              | 0.75                | 0.25     |                                  |
| Series 2           | BF4                  | 1              | 2               | 0.25                     | 0.75              | 0.25                | 0.75     |                                  |
|                    | BF5                  | 1              | 2               | 0.50                     | 0.50              | 0.50                | 0.50     |                                  |
|                    | BF6                  | 1              | 2               | 0.75                     | 0.25              | 0.75                | 0.25     |                                  |
| Series 3           | BF7                  | 2              | 1               | 0.25                     | 0.75              | 0.25                | 0.75     |                                  |
|                    | BF8                  | 2              | 1               | 0.50                     | 0.50              | 0.50                | 0.50     |                                  |
|                    | BF9                  | 2              | 1               | 0.75                     | 0.25              | 0.75                | 0.25     |                                  |

HPMC: Hydroxy propyl methyl cellulose; DMSO: dimethyl sulfoxide

**Formulation variables and physico-mechanical parameters**

The performance of dosage forms or drug delivery systems depends on many factors and effect of formulation variables is one among them. Many reports are available in literature which describes the special effects of

excipients/pharmaceutical vehicles on the enactment of concerned dosage forms.<sup>26-28</sup> Present investigation highlighted the influence observed on pH, mucoadhesive strength, swelling, residence time, and folding strength of buccal films upon varying the excipients. The result of characterization parameters are depicted in Table 2.

Table 2: Physico-mechanical characterization of buccal films containing simvastatin<sup>a</sup>

| Formulation series | Code | Film pH | Folding resilience (numbers) | Mucoadhesive strength (g) | Swelling Index <sup>b</sup> (%) | Drug content (%) | <i>In vitro</i> residence time <sup>c</sup> (min) |
|--------------------|------|---------|------------------------------|---------------------------|---------------------------------|------------------|---|
| Series 1           | BF1  | 6.2±0.2 | 72±2                         | 9.0±0.8                   | 12.3±1.5                        | 91.6±1.5         | 107.3±10.4  |
|                    | BF2  | 6.3±0.2 | 82±2                         | 8.3±0.4                   | 11.3±0.5                        | 87.9±2.6         | 108.3±8.6   |
|                    | BF3  | 5.9±0.4 | 87±3                         | 7.6±0.6                   | 13.3±0.5                        | 92.6±1.6         | 98.3±7.2  |
| Series 2           | BF4  | 5.8±0.1 | 75±4                         | 14.6±1.7                  | 20.0±2.0                        | 96.0±1.0         | 75.6±6.1  |
|                    | BF5  | 6.3±0.1 | 71±3                         | 13.5±0.8                  | 19.0±1.0                        | 94.6±3.0         | 71.0±9.6  |
|                    | BF6  | 6.1±0.2 | 76±3                         | 14.0±1.3                  | 17.3±3.0                        | 93.0±2.4         | 75.0±9.5  |
| Series 3           | BF7  | 6.2±0.2 | 96±3                         | 10.6±1.1                  | 16.0±1.0                        | 97.5±3.1         | 112.6±11.0  |
|                    | BF8  | 5.9±0.5 | 100±2                        | 11.2±2.0                  | 15.6±1.5                        | 94.9±1.6         | 120.0±10.0  |
|                    | BF9  | 6.0±0.5 | 108±6                        | 11.6±2.1                  | 16.2±0.6                        | 96.2±1.7         | 111.0±7.9   |

a: values are expressed as Mean ± SD (n = 3); b: swelling index of film after 4 h; c: time at which film was eroded or detached from mucosal surface

pH is one of the important parameter in buccal formulations as extreme high or low pH would cause irritation in the buccal region. Therefore pH around the neutral range is desirable for such formulations. Despite of different ingredients, the pH of buccal films were in the range of 5.8 ± 0.1 to 6.3 ± 0.1. The results showed that the prepared films were suitable for buccal administration as the pH of buccal region is nearly 6.5 (Table 2).<sup>10, 29</sup>

Mechanical strength is a very much crucial issue for any type of dosage forms. It has got very significant prospects as far as industrial requirement is concerned. Any cut, wear and tear or damage during handling or transportation is a big challenge; hence this is very critically evaluated. As friability is the official evaluation of tablets to ensure mechanical strength, folding resilience/endurance is the evaluation parameter of films/patches. As described in the material and method section, it is the number of times a film could be folded at a same place without cracking/breakage. Developed films of all 9 batches exhibited varying folding resilience. It was found to be in the range of 71 ± 3 to 108 ± 6 (Table 2). Here we have started experiencing the change in the evaluation parameters with the change in the formulation variables. Folding resilience is a function of amount of polymers as well as other ingredients, especially plasticizer. In our present study we have used two different plasticizer namely glycerol and propylene glycol in different concentrations. In the first series of films, it was observed that with the increasing concentration of propylene glycol and decreasing order of glycerol, folding resilience increases. It suggests that propylene glycol has additive effect on the same

parameter. Similar trend was also seen in the third series. The second series of films exhibited lower folding resilience which might be attributed to the effect of higher amount of Carbopol as compared to other series. BF9 (series 3) showed highest folding resilience (108 ± 6) and this may be due to the higher concentration of HPMC and propylene glycol making the film more flexible in nature. Some authors also studied film strength by using texture analyzer instead of folding resilience as a more precise method but this method is also well practiced by researchers.<sup>13, 14, 25</sup>

Buccal film is intended to be delivered by buccal route for either local or systemic action. In either case, it has to be adhered to the buccal mucosa for a prolonged period of time. Therefore, it must display good mucoadhesive characteristics. To impart mucoadhesive properties, Carbopol 940 (polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol) was used in the film formulations. Further, to examine the effect of this polymer on mucoadhesion and other parameters, it was used in same concentration in series-1 and 3 but in series-2 the concentration of Carbopol was double than previous series. Second series of films (BF4, BF5 and BF6) have shown stringer mucoadhesive properties. The maximum mucoadhesive strength was recorded for BF4 (14.6 ± 1.7) and BF6 (14.0 ± 1.3). It was interesting to note that there was no noteworthy effect of either penetration enhancer or plasticizer in the mucoadhesive strength of films. The better results for films of series 2 in comparison to series 1 and 3 are clearly due to the higher concentration of Carbopol. Series 3 showed better mucoadhesive potential

than series 1 although both series were having same concentration of Carbopol. This might be attributed to the higher concentration of HPMC in the third series than first series. HPMC is also having some extent of mucoadhesive properties.<sup>30</sup> New instrumental techniques are also available for the assessment of mucoadhesive strength, but the currently reported method is also a very popular method for the determination of mucoadhesive potential.<sup>25, 31, 32</sup>

Absorption of water and swelling are the imperative characteristics in the mucoadhesive formulations. The developed formulations were evaluated for swelling properties. Higher swelling was observed in the second series and Carbopol was responsible for such behavior of buccal films. Further, it was seen in second series that swelling index was increased with the rise in concentration of glycerol. BF4 was reported to show highest swelling index  $20.0 \pm 2.0\%$  at 4 h of experiment (Table 2). Swelling index tells about the integrity of mucoadhesive films as excessive swelling might cause the film to get eroded, at the same time inadequate swelling may cause less drug release. Swelling of polymer matrix cause the drug to diffuse through the swelled polymeric hydrogel and it is one of the rate limiting steps in drug release/permeation.<sup>33</sup>  
<sup>34</sup> All the film formulations exhibited adequate swelling and did not erode out which was an indication of good quality of film suitable for buccal administration. It has been observed that the polymers Carbopol and glycerol have central role as formulation variables in swelling behavior of films.

Dispersion of drug in the polymeric matrix is crucial as it determines the therapeutic effect after administration. Drug content is therefore an important parameter to be examined for film formulations. All the developed films were investigated for the drug content and it was found to be in the range of  $87.9 \pm 2.6$  to  $97.5 \pm 3.1\%$  (Table 2). Smooth surface of film as revealed by SEM photomicrograph also confirms the uniform distribution of drug and polymers. Smooth and even surface also helps in the proper adhesion of film to the site of action (buccal mucosa).<sup>35</sup>

Residence of film on the mucosal surface decides the success of therapeutic regimen. Unless the film will have adequate residence as well as contact with the buccal mucosa, therapeutic level of drug cannot be reached.<sup>36</sup> In order to ensure stay of film for sufficient time, residence time evaluation was performed. Film BF8 (third series) showed highest residence time i.e.  $120.0 \pm 10.0$  min (Table 2), rather all the films in third series have shown better

results in comparison to 2nd and 1st series. It was seen that stronger mucoadhesion was recorded with films in the second series but due to higher hydration (swelling index), these films could not stay longer with the mucosal surface. High concentration of Carbopol and consequently higher hydration might be the reason for lower residence time of films in second series. Additionally, it was also observed that equal proportion (1:1, BF7, Table 1) of propylene glycol and glycerol was showing good result. Higher concentration of either of the aforementioned excipients had resulted in to alteration in residence time of films.

Based on the results observed from the physico-mechanical characterization (Table 2) of films, the third series was selected as the best formulations. These series were containing 2:1 ratio of HPMC and Carbopol, which was found suitable in all characterization parameters. In this series BF7, BF8 and BF9 film formulations exhibited variance in their performance against evaluation parameters which was attributed to the diverse concentration of formulation variables. Further, these films were subjected to drug release/permeation characterization as well as stability analysis.

### **Effect of formulation variables on in vitro drug release and ex vivo drug permeation**

Investigating the effect of formulation variables on in vitro drug release and ex vivo drug permeation was one of the objectives of present dissertation. Films of series 3, BF7, BF8 and BF9 were subjected to the release/permeation studies and data were fitted to different kinetic models such as zero order, first order, Higuchi and Korsmeyer-peppas models. The results are presented in Table 3.

**Table 3:** Drug release/permeation kinetics of buccal films (Third series; BF7, BF8 and BF9)

| Kinetic model                  | Formulation code | Correlation co-efficient ( $r^2$ ) |             |         | Korsemayer-Peppas ( $n$ ) | Mechanisms |
|--------------------------------|------------------|------------------------------------|-------------|---------|---------------------------|------------|
|                                |                  | Zero Order                         | First Order | Higuchi |                           |            |
| <i>In vitro</i> drug release   | BF7              | 0.9885                             | 0.9155      | 0.9901  | 0.4248                    | Fickian    |
|                                | BF8              | 0.9944                             | 0.8748      | 0.9665  | 0.3978                    | Fickian    |
|                                | BF9              | 0.9920                             | 0.9018      | 0.9822  | 0.4100                    | Fickian    |
| <i>Ex vivo</i> drug permeation | BF7              | 0.9670                             | 0.9939      | 0.9485  | 0.4490                    | Fickian    |
|                                | BF8              | 0.9958                             | 0.9863      | 0.9822  | 0.4294                    | Fickian    |
|                                | BF9              | 0.9668                             | 0.9565      | 0.9974  | 0.4252                    | Fickian    |

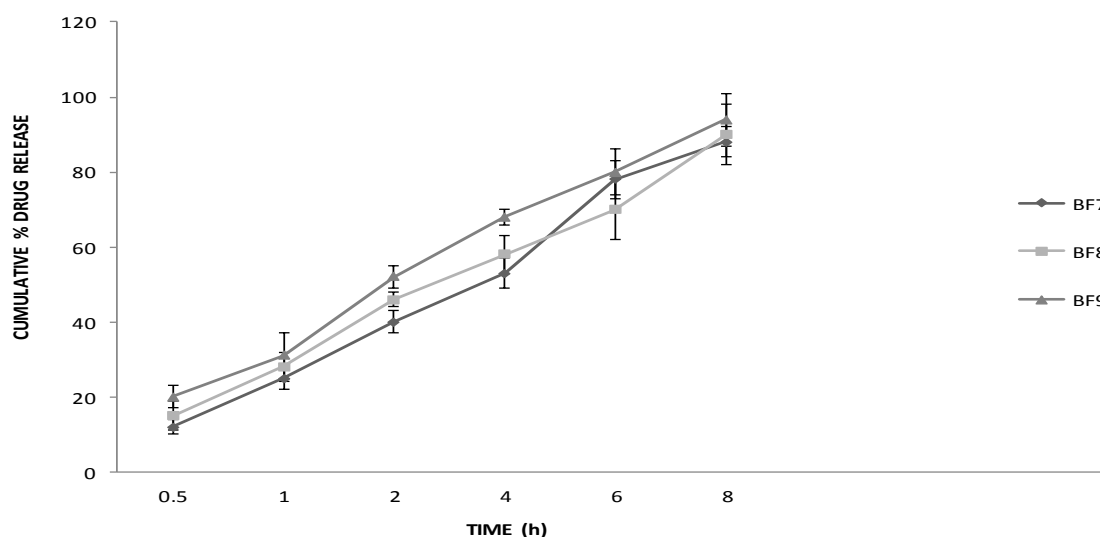


Figure 1 (a): In vitro zero order drug release kinetic plot

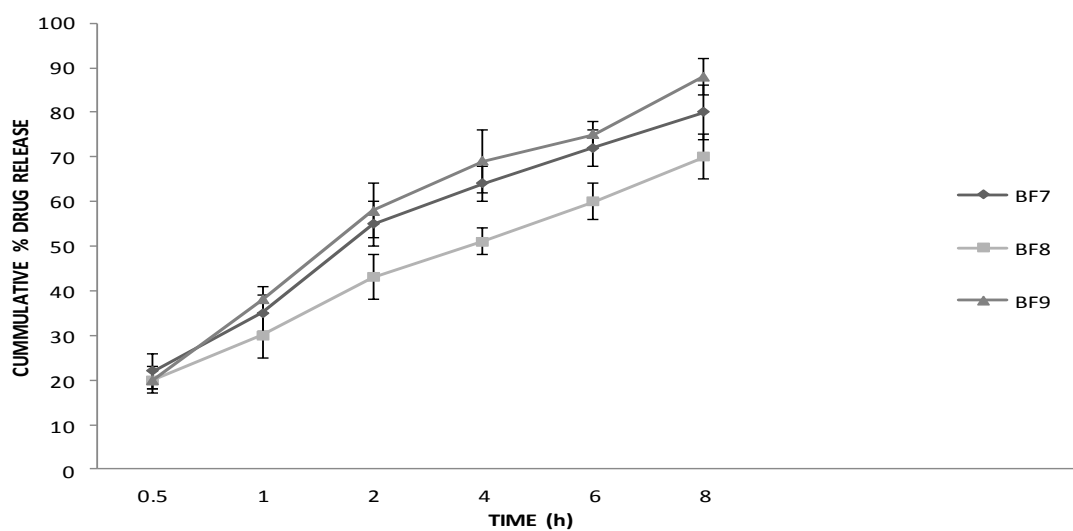


Figure 1 (b): Ex vivo zero order drug permeation kinetic plot

**Figure 1 (a, b):** Zero order release/permeation kinetic of films (Third series; BF7, BF8 and BF9).

All films showed more than 90% drug release/permeation in 8 h and followed zero order release/permeation as revealed by the correlation co-efficient ( $r^2$ ) values (Table 3). This shows that the drug from the polymer matrix is released in a sustained manner. Such behavior is desirable in film/patch formulation.<sup>16, 36</sup> The zero order drug release and permeation plots are shown in Figure 1 (a) and (b) respectively. Film BF9 exhibited  $94 \pm 7\%$  in vitro drug release and  $88 \pm 4\%$  ex vivo drug permeation. These films were further found to be following Higuchi's model (Table 3) indicating the diffusion mechanism. After adequate hydration, the polymer matrix developed a hydrogel layer and through this layer drug diffuses out to the dissolution medium. As polymers in all film are in same ratio, it was assumed that other variables especially the penetration enhancer would show effect in drug release/ permeation. In case of in vitro drug release there were not much difference in the release of drug from polymer matrix (BF7:  $88 \pm 4$ ; BF8:  $90 \pm 8$ ; BF9:  $94 \pm 7\%$ ). At the contrary,

there was a remarkable difference in the permeation of drug from the goat buccal mucosa in ex vivo studies (BF7:  $80 \pm 5$ ; BF8:  $70 \pm 6$ ; BF9:  $88 \pm 4\%$ ). The decrease in drug permeation in comparison to in vitro drug release is attributed to the complex nature of goat buccal mucosa.<sup>18</sup> In the ex vivo drug permeation studies, it was clearly observed that higher concentration of dimethyl sulfoxide facilitated drug permeation than eucalyptol oil. The drug release/permeation was following the Fickian type diffusion mechanism which was confirmed from the Korsmeyer-Peppas plot ( $n$  values, Table 3). Stability studies revealed that the film BF9 was intact throughout the storage period. There was no substantial difference in the characterization parameters as well as drug release behavior in comparison to the freshly prepared film. A comparative photomicrograph is shown in Figure 2(a) and 2(b) where both the freshly prepared as well as stored films are shown.

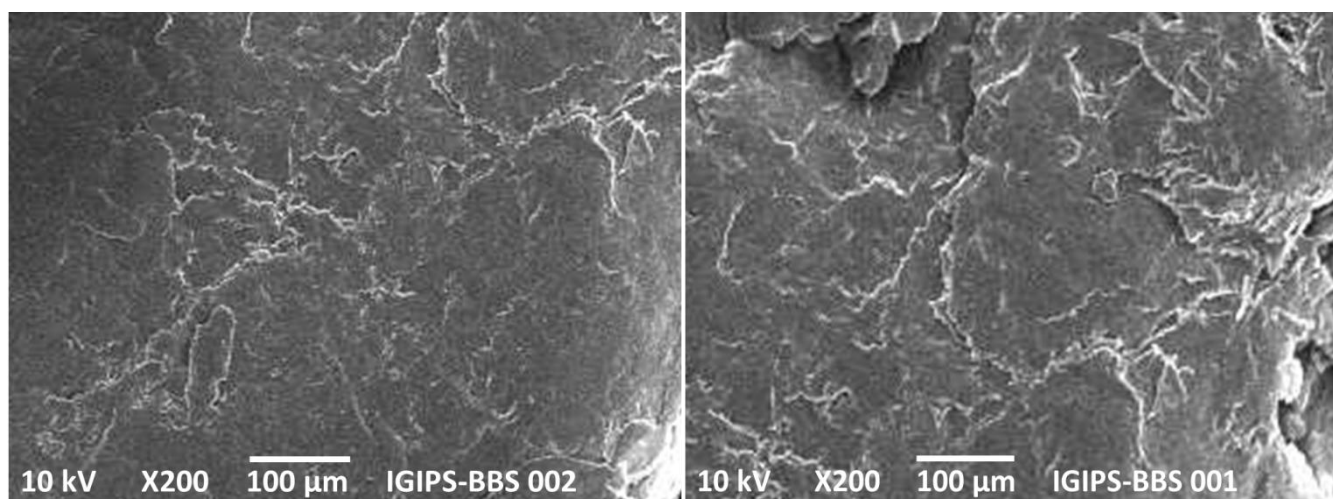


Figure: 2 (a)

Figure 2: (b)

**Figure 2:** SEM photomicrographs of films (a) freshly prepared film (b) film after 6 months of storage at  $22 \pm 1^\circ\text{C}$

### Bucco-compatibility of films

As described in the materials and methods section, the developed films were examined for any potential growth inhibitory effect on the pro-biotic microorganisms. The net zone of growth inhibition against the pro-biotic bacteria *Lactobacillus acidophilus*, *Bifidobacterium infantis* and *Lactobacillus rhamnosus* were found to be  $2 \pm 1$ ,  $3 \pm 1$  and  $2 \pm 1$  mm, which indicated that there was no considerable inhibitory effect of the films on the growth of the tested pro-biotic bacteria. Bucco-compatibility is a very important aspect in buccal drug delivery. Any formulation which is intended for prolonged adherence/stay in the

buccal environment must be compatible with the buccal micro-flora.

### Conclusion

In conclusion, formulation variables employed in film formulation have imperative effect on the performance of buccal films. Polymers (HPMC and Carbopol) and plasticizers (propylene glycol and glycerol) have pivotal effect on the physico-mechanical parameters whereas penetration enhancers (eucalyptol oil and dimethyl sulfoxide) have considerable effect on the drug release/permeation behavior of films. Developed film was



compatible with the buccal micro-flora. The novel, bucco-compatible film of simvastatin may be employed as a suitable alternative in lipid lowering medication after clinical confirmation.

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### **Conflict of interest**

All authors involved in the present investigation declare no conflict of interest.

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