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# Comparative Study of Various Permeation Enhancers for Development of Sumatriptan Succinate Buccal Tablet

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## ABSTRACT

The aim of the present study was to prepare buccoadhesive sustained release tablets of sumatriptan succinate using various permeation enhancers to release the drug for extended period of time with reduction in dosing frequency. In the present work sumatriptan succinate was used as a model drug and interaction studies performed using FTIR spectroscopy and DSC revealed that there was no drug, polymer and permeation enhancer interaction. Fulvic acid was extracted from shilajit by using resins. Fulvic acid was characterized by various spectroscopic techniques. Buccoadhesive sustained release tablets of sumatriptan succinate with various permeation enhancers were prepared by direct compression method using bioadhesive polymers like Carbopol 934 and HPMC K100M. The physical characteristics like surface $p^H$, swelling index, *in vitro* mucoadhesion time, *in vitro* mucoadhesion strength, *in vitro* drug release study and *in vitro* permeation study. The *in vitro* release study showed 99.88%, 99% and 99.40% of drug release with fulvic acid, chitosan and beta cyclodextrin respectively. The permeation study showed 90%, 82% and 78% of drug permeated with fulvic acid, chitosan and beta cyclodextrin respectively. Sumatriptan succinate release from the buccoadhesive system was extended and exhibited a non fickian drug release kinetics approaching to first order as the values of release rate exponent varied between 0. 97 to 0.99 resulting in a regulated and complete release until 8 hours.

**Keywords:** - Buccal drug delivery system, Sumatriptan succinate, Fulvic acid, In-vitro drug release study, In-vitro permeation study.

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## INTRODUCTION

Amongst the various routes of drug delivery, oral route is the most preferred by the patient and the doctors. However, oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug absorption[1].

The permeation of hydrophilic drug through membrane is one of the major limiting factors for the development of bioadhesive buccal delivery devices. The epithelium that lines the buccal mucosa is a main barrier for the absorption of drugs[2]. In order to improve buccal absorption, several approaches have been introduced. Increased permeation of the drug through the buccal membrane and prevention of the drug degradation by enzymes was achieved by changing the physicochemical properties of the drug[3]. Alternatively, improving the bioadhesion and release characteristics of buccal delivery devices increases the amount of drug available for absorption[4]. The incorporation of absorption enhancers to the buccal formulation is one interesting approach. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers[5]. Different types of potential permeation enhancers have been studied for buccal route to increase the penetration of drugs [6, 7].

Sumatriptan succinate, a 5- HT receptor agonist, has been widely used in the treatment of migraine. It belongs to BCS Class III with high water solubility but poor permeability. Sumatriptan succinate undergoes the first pass metabolism with approximate systemic bioavailability of 14%, following oral administration. Sumatriptan succinate is suitable candidate for administration by the buccal route due to its short half life (2 hours) as well as a low molecular weight[8].

Shilajit is a blackish-brown exudation obtained from steep rocks. Shilajit is a complex mixture of humic substances and of plants and microbial metabolites. It consists of benzoic acid, hippuric acid, fatty acids, resins, waxy materials, albinoids and vegetable matter. Shilajit mainly comprised of humus (60-80 %) along with other constituents. Humic substances consist of humic acid, fulvic acid and humin. The major physiological action of shilajit was found to be due to the presence of the bioactive dibenzo- alpha- pyrones along with humic acid and fulvic acid, which

act as carrier molecules for the active ingredients [9, 10]. Fulvic acid has polymeric structure having large number of voids and pores in its structure with a number of functional groups which are capable of forming inclusion complexes. It has been reported that fulvic acid acts as a carrier molecule for the in-vivo transportation of bioactive substances. On the basis of this, study was planned to explore fulvic acid as permeation enhancer for buccal drug delivery. Thus, objective of the present study was to compare various permeation enhancers for buccal delivery of sumatriptan succinate. Fulvic acid acts as carrier molecules for active substances [11, 12, 13].

## MATERIALS & METHODS

All the chemicals were obtained from commercial supplier and used as received: Sumatriptan succinate (Dr. Reddy's Laboratories Limited, Hyderabad, India), Carbopol 971P (Noveon Pharmaceutical Limited, Mumbai, India), HPMC K100M (Colorcon Asia Limited, Goa, India), Avicel pH 102 (Colorcon Asia Limited, Goa, India), Chitosan (Pacific Marine Chemicals Limited, Cochin, India), PVP K30 (BASF India Limited, Mumbai), Beta- cyclodextrin (Dr. Reddy's Laboratories, Hyderabad, India) and Magnesium stearate (S.D.Fine Chemicals Limited, Mumbai, India). Fulvic was extracted from shilajit in laboratory. Resins were purchased from Thermax Limited, India. All the other reagents and chemicals were used of analytical grade.

**Extraction of Fulvic Acid from Shilajit**

Raw shilajit (200 gm) was extracted with 500 ml of organic solvents of increasing polarity viz., chloroform, ethyl acetate and methanol to remove the bioactive components. 50 gm of extracted shilajit was then dispersed in 500 ml of 1 N NaOH with intermittent shaking in the presence of nitrogen at room temperature for 24 hours. The suspension was filtered out and the filtrate was acidified with the concentrated hydrochloric acid to a pH of less than 3. The solution was allowed to stand overnight. The humic acid was obtained as coagulate which was separated out by filtration. The filtrate containing fulvic acid was extracted by shaking the filtrate with 25 gm of macroporous ion exchange resin, (TULSION ADS- 400 from M/S Thermax Limited, India) for 5 -10 minutes in order to adsorb the fulvic acid on the macroporous resin. The adsorbed fulvic acid on the resin was then eluted out with 50 ml of 0.1 N NaOH solutions. The process of extraction was repeated 6-7 times using the same macroporous resin for the complete elution of fulvic acid. The resulting solution was shaken with 15 gm of hydrogen saturated cation exchange resin (INDION 225H from M/S Thermax Limited, India) for 5 minutes in order to exchange sodium ion with the hydrogen ion. The obtained fulvic acid solution was then dried in oven to get amorphous powder [14].

**Preparation of buccoadhesive tablets:**

The buccoadhesive tablets were prepared using different polymers either alone or in combinations with varying ratios as summarized in Table 1. Tablets were prepared by wet granulation method involving following steps. The drug and buccoadhesive polymer mixture was prepared by homogeneous mixing followed by granulating with binder solution. The granules were dried and sieved through sieve no. 20. The lubrication of dried granules was carried with magnesium stearate. The dried granules were compressed on 3 mm flat punch machine using single punch tablet compression machine (Rimek Minipress-2, Ahemadabad). Each tablet weighed 100 mg with a thickness of 2.9 to 3.0 mm.

**Table 1: Composition of Sumatriptan Succinate Buccoadhesive Tablets with Various Permeation Enhancers**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Sumatriptan succinate | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| HPMC K100M | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Carbopol 971P | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Avicel pH 102 | 32.4 | 30.8 | 29.2 | 32.4 | 30.8 | 29.2 | 32.4 | 30.8 | 29.2 |
| Fulvic acid | 1% | 2% | 3% | - | - | - | - | - | - |
| Chitosan | - | - | - | 1% | 2% | 3% | - | - | - |
| Beta Cyclodextrin | - | - | - | - | - | - | 1% | 2% | 3% |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Total | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**EVALUATION OF BUCCOADHESIVE TABLETS**

All tablets were evaluated for different parameters such as surface pH, swelling index, in-vitro bioadhesion study, ex-vivo mucoadhesion time, *in-vitro* drug release and *in-vitro* drug permeation across buccal mucosa.

**Surface pH Study**

The surface pH of the buccal tablet was determined in order to study any side effects after administration of tablet. As an acidic or alkaline pH may irritate the buccal mucosa, so for that we try to maintain the surface pH close to neutral. The method adopted by Bottenberg *et al.* was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.4 ± 0.005) for 2 hours at room temperature. The pH was determined by bringing the electrode in contact with tablet surface and allowing the surface to equilibrate for 1 minute [15].

**Swelling Study**

In this study, tablets were weighed individually (designated as $w_1$) and placed separately in petri dishes containing phosphate buffer pH 6.8. At regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8 hr),

samples were removed from the petri dish and excess water was removed carefully by using tissue paper. The swollen tablets were reweighed ($w_2$)13. The swelling index of each system was calculated using equation (1) [16]:

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} \times 100 \qquad (1)$$

**In- vitro Bioadhesion study**

The in-vitro bioadhesion study was carried out using a modification of bioadhesion test assembly described by Gupta *et. al*. Bioadhesion test apparatus employed for the purpose was a modification of the modified double beam physical balance. Sheep buccal mucosa was used as the model membrane for the measurement of bioadhesive strength. It was fixed to the glass vial using a thread. The vial was lowered into the jacketed glass container filled with buffer pH 6.8 and maintained at 37±1°C. Before carrying out the investigation, the jacketed glass container containing beaker was kept below the right hand setup of the assembly. The tablet was stuck to the lower side of the beaker using acrylate adhesive. The assembly was kept undisturbed for 1 min and the weights were slowly added to the left hand side till the tablet just detached from the membrane surface. The bioadhesion force was calculated in terms of force (gm) required to detach the tablet from the membrane[17].

**Ex- vivo Mucoadhesion Time**

The ex-vivo mucoadhesion time was examined after application of the tablet on freshly cut sheep buccal mucosa over glass slide[18]. The sheep buccal mucosa was tied on the glass slide and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The dissolution flask was filled with 200 ml of phosphate buffer pH 6.8 and kept at 37 ± $1^0$ C. After 2 minutes, a slow stirring rate was applied to simulate the buccal cavity environment and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time.

***In- vitro* Drug Release Study**

The United State Pharmacopoeia XXIII rotating paddle method was used to study the drug release from the tablet. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release was performed at 37 ± 0.5 $^0$ C, with a rotation speed of 50 rpm. Samples of 5 ml were withdrawn at predetermined time interval and replaced with fresh medium. The samples were filtered through 0.2 µm whatman filter paper and analyzed with HPLC instrument (Younglin, Korea) by using suitable mobile phase [19].

***In- vitro* Drug Permeation Study**

The *in- vitro* permeation study of sumatriptan succinate through sheep buccal mucosa was performed using a Franz Diffusion cell at 37 ± 0.2 $^{0}$ C. Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. The buccal tablets with various permeation enhancers were placed with the core facing the buccal mucosa and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment (15 ml capacity) was filled with phosphate buffer pH 7.4 and the uniform concentration in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. One milliliter samples were withdrawn at predetermined time intervals and amount of sumatriptan succinate was analyzed with HPLC (Younglin, Korea) by using suitable mobile phase[20].

## RESULTS AND DISCUSSION

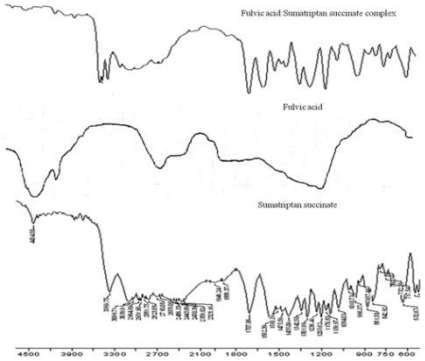


**Figure 1. IR spectrum of Sumatriptan succinate (A), Fulvic acid (B), Sumatriptan succinate: Fulvic acid complex (C)**

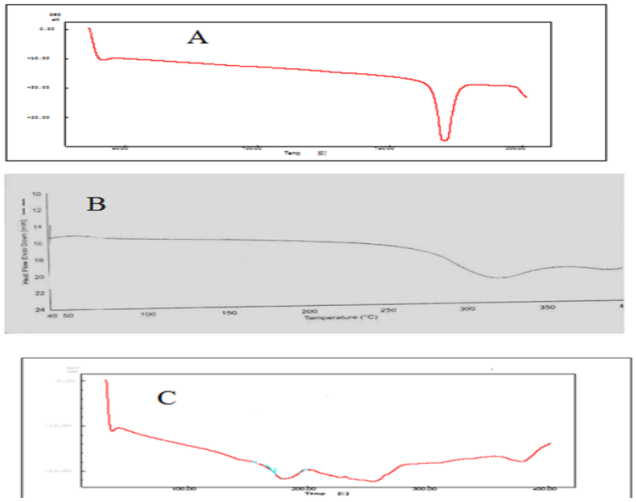


**Figure 2. DSC thermogram of Sumatriptan succinate (A), Fulvic acid (B), Sumatriptan succinate: Fulvic acid complex (C)**

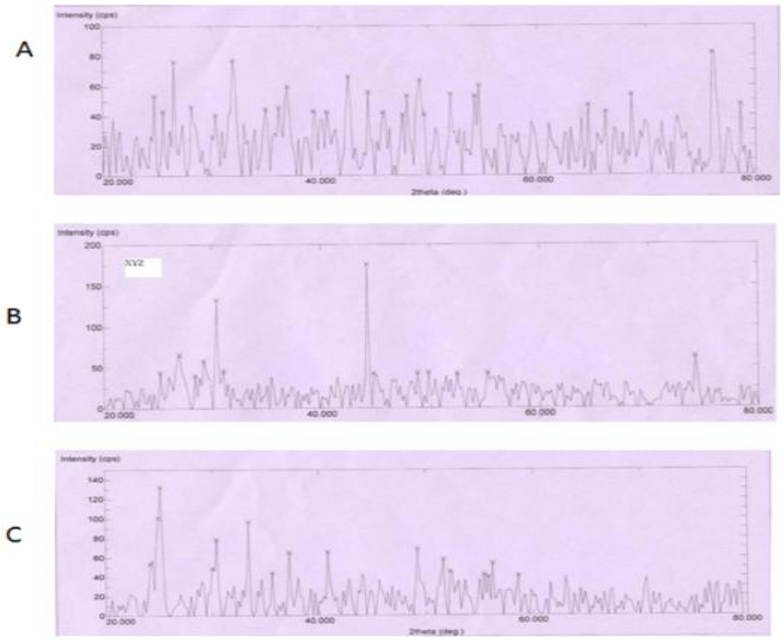


**Figure 3. XRD spectrum of Sumatriptan succinate (A), Fulvic acid (B), Sumatriptan succinate: Fulvic acid complex (C)**

**Evaluation of Tablet**

CP and HPMC K100M were selected as the biodhesive polymer because of their excellent bioadhesive properties. The buccoadhesive drug delivery system of sumatriptan succinate was prepared and characterized *in-vitro* by studying surface pH, swelling index, in-vitro bioadhesion study, ex-vivo mucoadhesion time, *in-vitro* drug release and *in-vitro* drug permeation across buccal mucosa.

**Surface pH**

The study of surface pH is essential in order to prevent irritation to mucosa due to acidic and alkaline nature of tablet. It is kept near to neutral. The results of surface pH study of sumatriptan buccal tablet with various permeation enhancers are as shown in Table 2.

**Table 2: *In-Vitro* Surface PH Study of Buccal Tablets of Sumatriptan Succinate with Various Permeation Enhancers**

| Batch Code | *In- vitro* Surface pH |
|---|---|
| F1 | 6.8 ± 0.50 |
| F2 | 7.0 ± 0.80 |
| F3 | 7.2± 0.65 |
| F4 | 6.6 ± 1.01 |
| F5 | 6.7 ± 1.20 |
| F6 | 6.3 ± 1.00 |
| F7 | 6.5± 0.60 |
| F8 | 6.8± 0.80 |
| F9 | 6.7 ± 0.74 |

**Swelling Study**

Appropriate swelling behavior of a buccal adhesive system is essential for prolong and uniform release of the drug and effective mucoadhesion[21]. The rate of swelling was inversely proportional to the CP contents of tablets. The maximum swelling index was found higher in batch F3 and the lowest in batch F8 which is as shown in Figure.4.

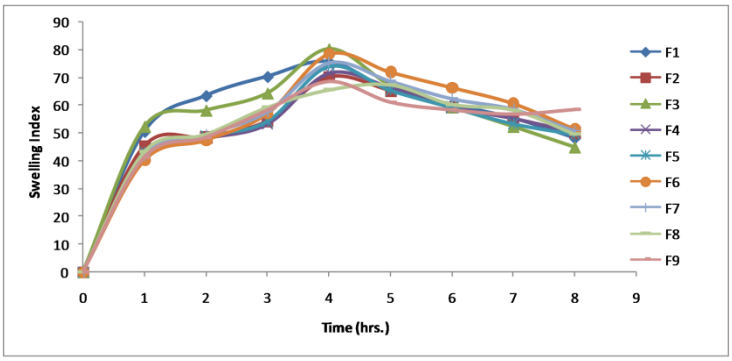


**Figure 4.Swelling index study of sumatriptan succinate mucoadhesive tablets with various permeation enhancers in 6.8 pH buffer**

**In-vitro Mucoadhesion study**

The in-vitro bioadhesive strength tablet was determined for different contact times, using sheep buccal mucosa. The high mucoadhesive strength of CP may be due to formation of secondary mucoadhesive bonds with mucin[22]. The batch F3 showed good mucoadhesive strength. The mucoadhesive strength of various batches is as shown in Table 3.

**Ex-vivo Mucoadhesion Time**

The mucoadhesive time on buccal mucosa ranged from 8 to 12 hours as shown in **Table 3**.

**Table 3: *In-Vitro* Mucoadhesive Study of Buccal Tablets of Sumatriptan Succinate With Various Permeation Enhancers**

| Batch Code | Ex- vivo Mucoadhesion Time (hrs) | Mucoadhesive Strength (gram) |
|---|---|---|
| F1 | 10.5 ± 0.50 | 36.46 ± 1.88 |
| F2 | 11 ± 0.80 | 33.22 ± 1.20 |
| F3 | 12 ± 0.65 | 36.71 ± 2.57 |
| F4 | 10 ± 1.10 | 28.69 ± 1.14 |
| F5 | 10 ± 1.20 | 27.46 ± 2.36 |
| F6 | 9.5 ± 1.00 | 26.01 ± 1.23 |
| F7 | 9 ± 0.60 | 25.01 ± 0.86 |
| F8 | 8 ± 0.80 | 24.34 ± 1.25 |
| F9 | 8.7 ± 0.74 | 23.17 ± 2.10 |

***In- vitro* Drug Release**

*In-vitro* drug release was proportional to HPMC content and inversely proportional to CP content

The higher the uptake of water by the polymer, greater the amount of drug diffused from the polymer matrix. All the tablets (F1-F9) remain intact during the 12- hour period. *In-vitro* drug release study of tablet with various permeation enhancers is as shown in Figure. 5.

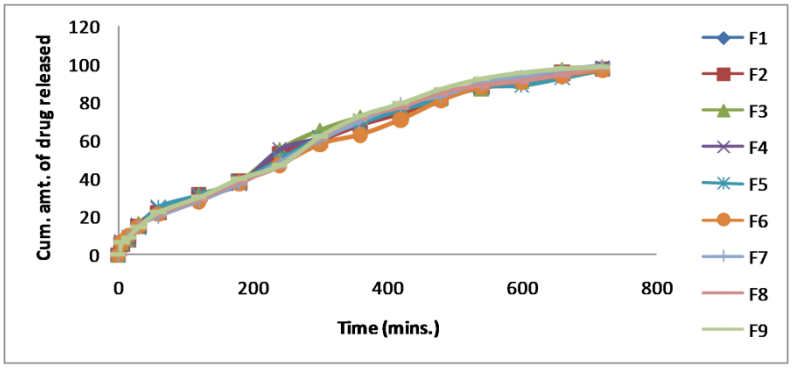


**Figure 5: Dissolution study of sumatriptan succinate mucoadhesive tablets with various permeation enhancers in 6.8 pH buffer**

**Permeation Study across Buccal Mucosa**

The permeation study of bucccoadhesive system was carried out using sheep buccal mucosa. The permeation study was carried out for system with various permeation enhancers. Formulations F1 to F9 were subjected to an *in-vitro* buccal permeation study using a Franz Diffusion Cell. The results of permeation studies are as shown in Figure.6.

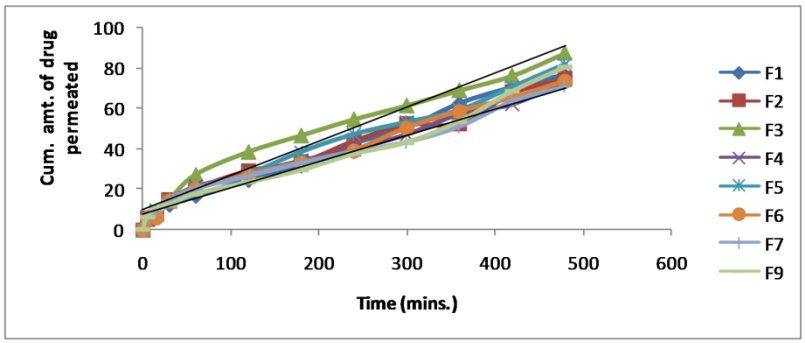


**Figure 6:-Permeation study of sumatriptan succinate mucoadhesive tablets with various permeation enhancers in 6.8 pH buffer**

**Release Kinetic Study**

The permeation rate profile for the optimized formulation F3 was further analyzed for release order. A plot of the drug permeated and time yielded a straight line, indicating a 1$^{st}$ order release with a release constant of 0.9776 h$^{-1}$.

For all the batches, the values of n ranged from 0.5032 to 0.7034 (Table-4), indicating non-fickian release.

**Table 4: Kinetics Data of Sustained Release Tablet In 6.8 PH Buffer with Various Permeation Enhancers**

| Formulation Code | Zero order | First order | Higuchi | Korsmeyer Peppas | Korsmeyer Peppas |
|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | n |
| F1 | 0.8189 | 0.9719 | 0.9845 | 0.9825 | 0.84 |
| F2 | 0.8634 | 0.9827 | 0.9802 | 0.9876 | 0.95 |
| F3 | 0.8915 | 0.9909 | 0.9901 | 0.9774 | 0.70 |
| F4 | 0.8037 | 0.9807 | 0.9885 | 0.9811 | 0.83 |
| F5 | 0.8374 | 0.9892 | 0.9735 | 0.9976 | 0.93 |
| F6 | 0.7972 | 0.9762 | 0.9672 | 0.9842 | 0.89 |
| F7 | 0.7667 | 0.9927 | 0.9725 | 0.9776 | 0.79 |
| F8 | 0.7641 | 0.9725 | 0.9730 | 0.9886 | 0.88 |
| F9 | 0.8798 | 0.9889 | 0.9740 | 0.9854 | 0.90 |

## CONCLUSION

A buccoadhesive tablet of sumatriptan succinate using various permeation enhancers was developed successfully. The formulation was found to be having bioadhesive and swelling property due to presence of carbopol and HPMC. Fulvic acid containing tablet has shown enhancement in permeation of drug up to 90% across buccal mucosa as compared to the chitosan and beta cyclodextrin. From study it concludes that the fulvic acid act as best permeation enhancer as compared to chitosan and beta cyclodextrin.

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