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Application of Fulvic Acid as a Pemeation Enhancer for Buccal Drug Delivery of Sumatriptan Succinate

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ABSTRACT

The aim of the present study was to prepare buccoadhesive sustained release tablets of sumatriptan succinate using novel permeation enhancer 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 novel permeation enhancer were prepared by direct compression method using bioadhesive polymers like carbopol 934 and HPMC. The physical characteristics like surface pH, swelling index, *in vitro* mucoadhesion strength, *in vitro* drug release and *in vitro* permeation of formulated tablets were shown to be dependent on characteristics and composition of bioadhesive materials used. The *in vitro* release study showed 99.88% of drug release with fulvic acid, respectively. Fulvic acid containing tablet has shown enhancement in permeation of drug of 93 % in 12 hours across buccal mucosa in comparison with plain sumatriptan succinate tablet. 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, In-vitro permeation study

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INTRODUCTION

In recent years, delivery of therapeutic drugs through various transmucosal routes gained significant attention because of their first pass metabolism and instability in the acidic environment associated with oral administration[1]. Buccal drug delivery system is considered as a suitable alternative to oral route. Buccal devices provides direct entry of drug into the systemic circulation, thus avoiding the hepatic first pass metabolism, ensuring ease of administration and making it possible to terminate delivery when required[2]. A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for desired duration of time. In addition, it should release the drug in a unidirectional way towards mucosa in a controlled and predictable manner to produce the desired therapeutic effect[3, 4].

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[5].

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 [6, 7]. 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 explore fulvic acid as permeation enhancer for buccal delivery of sumatriptan succinate. Fulvic acid acts as carrier molecules for active substances[8, 9, 10].

MATERIALS & METHODS

Sumatriptan succinate was obtained as a gift sample from Dr. Reddy's Laboratory Limited, India. Carbopol 934 was provided by Noveon Pharmaceutical Limited, India. HPMC K4M was

as a gift sample from Colorcon Asia Limited, India. Microcrystalline cellulose and Magnesium stearate was procured from S.D.Fine Chemicals, India. Resins were purchased from Thermax Limited, India. All reagents and chemicals were used of analytical reagent 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 solution. 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[11].

Preparation of complex

Method Used: -

Solvent Evaporation:

Sumatriptan succinate: Fulvic acid complex (Ratio- 2:1) was prepared by dissolving the drug and fulvic acid in distilled water separately. The mixture was prepared by adding fulvic acid solution in sumatriptan succinate solution. The mixture was sonicated and the solvent was evaporated to dryness in round bottom flask using heating mental. The complex was dried in oven at 80^0 C and collected. The complex was sieved through sieve no-60 and was stored in dessicator until use.

Assay of Complex

The total 37.5 mg of complex (equivalent to 25 mg of sumatriptan succinate) was taken in 100 ml volumetric flask. It was dissolved in distilled water and its volume was make up to 100 ml with distilled water. Then prepared sample was analyzed by HPLC method.

Characterization of complex

The characterization of sumatriptan succinate: fulvic acid complex was done by means of FTIR,

DSC and XRD.

Fourier Transform Infrared spectroscopy (FTIR)

FTIR spectrum of the sample was recorded on shimadzu 8400 FTIR instrument using the KBr pellet technique. In that, 1 mg previously dried sample was mixed with 100 mg KBr and compressed into a pellet on an IR hydraulic press. Scanning was done from 4000 – 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Melting point of sample was determined by using DSC (shimadzu, Japan). The sample (5 mg) was sealed in aluminum foil and was scanned in the temperature range from 30^0 -300^0 C along with a reference sample as standard. The heating rate was 10 ^{0} C per minute under nitrogen atmosphere with a flow rate of 40 ml per minute to prevent thermo- oxidative degradation.

X- Ray Powder Diffractometry: The powder samples of about 1 mg were packed in x-ray holder. The x-ray diffraction patterns were recorded on a Rigaku- D/Max- 2500 PC diffractometer using Ni filter, cu Ka radiation, a voltage of 40 kV and a 300 mA current. The scanning rate was kept at 0.02^0/sec.

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 direct compression method involving two successive steps. The drug and buccoadhesive polymer mixture was prepared by homogeneous mixing followed by lubrication with magnesium stearate and mixed. The blended powder was then compressed on 3 mm flat punch machine using single punch tablet compression machine (Rimek Minipress-1, Ahemadabad). Each tablet weighed 100 mg with a thickness of 2.9 to 3.0 mm.

Table 1- Composition of Sumatriptan Succinate Buccoadhesive Tablets

Ingredients (mg)	F1	F2	F3	F4	G1	G2	G3	G4
Sumatriptan succinate	25	25	25	25	-	-	-	-
Sumatriptan succinate Fulvic Acid Complex	-	-	-	-	37.5	37.5	37.5	37.5
CP 934	10	10	10	10	10	10	10	10
HPMC K4M	40	30	20	10	30	20	10	05
Avicel	23	33	43	53	20.5	30.5	40.5	45.5
Magnesium stearate	2	2	2	2	2	2	2	2

Evaluation of buccoadhesive tablets

All tablets were evaluated for different parameters such as surface pH, swelling index, ex-vivo mucoadhesive strength, 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 tablets 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 to neutral. The method adopted by Bottenberg *et al.*[11] 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 [12].

Swelling Study

The swelling properties of drug were determined by placing the tablet matrices in the dissolution test apparatus containing 900 ml of phosphate buffer pH 6.8 at 37 ± 0.5 ^{0}C. The tablets were removed periodically from dissolution medium. After draining the water, weight gain, thickness and diameter of tablets were measured. Swelling characteristics were expressed in terms of % water uptake (WV %) and it is given by following equation (1),

(WV %)=(weight of swollen tablet – Initial weight of tablet)/ (Initial weight of tablet).....(1)

Ex-vivo Mucoadhesive strength

A modified balance method was used for determining the ex-vivo mucoadhesive strength [13, 14]. The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a vial, which was filled completely with phosphate buffer pH 6.8 and held left side of balance. The glass vial with rubber stopper was placed and tightly fitted in the center of glass beaker containing phosphate buffer (pH 6.8, 37 ± 0.1 ^{0} C) just touching the mucosal surface. The tablet was stuck to the lower side of the rubber side of the rubber stopper of the glass vial with the cyanoacrylate adhesive. The left and right pans were balanced by adding a 5 gm on the right hand side pan. When the 5 gm of weight was removed from the right hand pan, the left hand pan along with the tablet was lowered over the mucosa. The balance was kept in this position for 5 minutes. Water was added slowly at 100 drops/min to the right hand pan until the tablet detached from the mucosal surface. The weight (gram) required to detach from the mucosal surface gave the value of mucoadhesive strength.

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[15]. 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 (Table 2).

***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 [15].

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

The *in- vitro* buccal mucosa 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 permeation enhancer (i.e. Fulvic acid) and without permeation enhancer (i.e. Fulvic acid) 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[15].

RESULTS AND DISCUSSION

Previously various studies were carried out on Fulvic acid showing that it is having porous structure and having ability to incorporate drug molecules into its cavity and act as a carrier for the in-vivo transportation of drug molecules. The fulvic acid was characterized by UV spectroscopy, FTIR spectroscopy and XRD spectroscopy. Then sumatriptan succinate and fulvic acid complex was prepared by solvent evaporation method in the molar ratio 1:0.5 and characterized by FTIR spectroscopy, Differential Scanning Calorimetry and XRD spectroscopy

Characterization of complex

FTIR Spectroscopy

FTIR spectra of Sumatriptan succinate, Fulvic acid & Sumatriptan succinate complex are as shown in Figure 1. Sumatriptan succinate: fulvic acid complex prepared in molar ratio of 1:0.5 exhibited spectra where some of the characteristic peaks of sumatriptan succinate at 3373 and

2710 cm^{-1}were absent while some characteristic peaks of sumatriptan were found to be reduced in intensity. This indicates the complex formation between Sumatriptan succinate and fulvic acid.

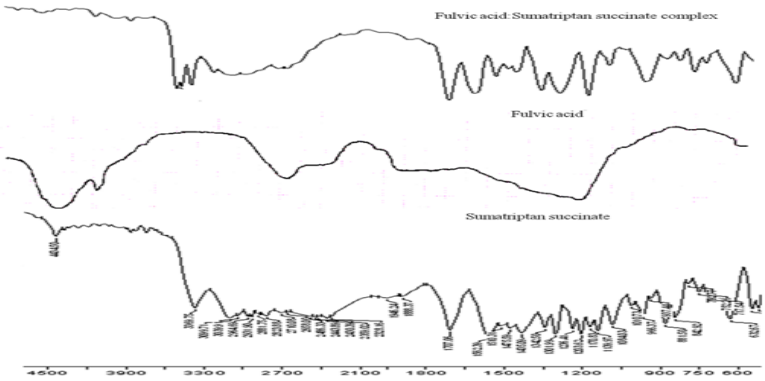

Figure 1. IR spectrum of Sumatriptan succinate (A), Fulvic acid (B), Sumatriptan succinate: Fulvic acid complex (C)

Differential Scanning Calorimetry (DSC)

DSC thermograms of Sumatriptan succinate, Fulvic acid & Sumatriptan succinate complex are as shown in Figure 2. DSC thermogram of Sumatriptan succinate: Fulvic acid complex was obtained in the temperature range of 30 to 400 ^{o}C. The sumatriptan succinate is having melting point 165-166^{o}C and Fulvic acid is having melting point 312- 314 ^{o}C. The sample showed very broad endothermic peak at about 165.18^{o}C thus it indicates the inclusion of sumatriptan succinate in fulvic acid. It can be concluded that there is formation of sumatriptan succinate: Fulvic acid complex in 1:0.5 molar ratio.

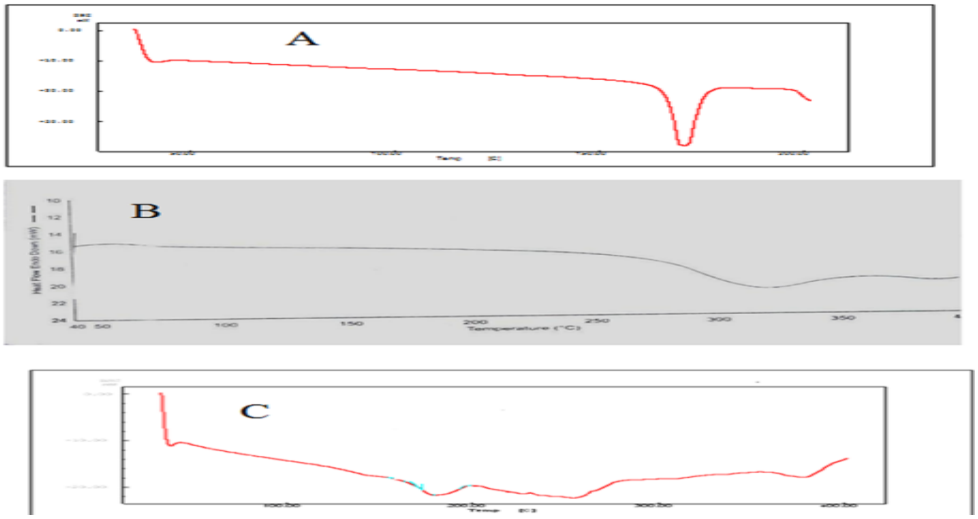

Figure 2. DSC thermograms of Sumatriptan succinate (A), Fulvic acid (B), Sumatriptan succinate: Fulvic acid complex (C)

X - Ray Diffraction Spectroscopy

XRD spectra of Sumatriptan succinate, Fulvic acid & Sumatriptan succinate complex are as shown in Figure 3. XRD pattern of complex prepared in molar ratio of 1:0.5 exhibited an amorphous nature, characterized by the absence of intense peak of sumatriptan succinate, indicating formation of complex between two in this ratio 1:0.5.

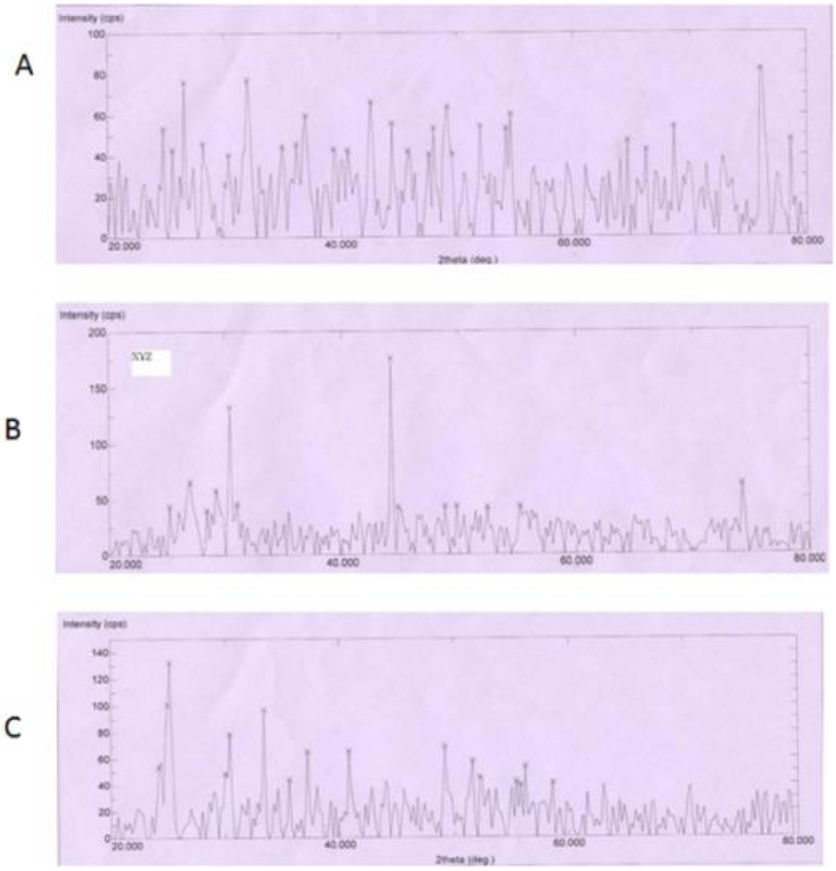

Figure 3. XRD spectrum of Sumatriptan succinate (A), Fulvic acid (B), Sumatriptan succinate: Fulvic acid complex (C)

Evaluation of Tablet

CP and HPMC K4M were selected as the bioadhesive 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, ex-vivo mucoadhesive strength, ex-vivo mucoadhesion time, *in-vitro* drug release and *in-vitro* drug permeation across buccal mucosa.

The surface pH of all the tablets was within a range of 5.78 to 6.89.

Swelling Study

Appropriate swelling behavior of a buccal adhesive system is essential for prolong and uniform release of the drug and effective mucoadhesion[16]. The rate of swelling was inversely proportional

to the CP contents of tablets. The maximum swelling index was found in batch G3 with permeation enhancer i.e. fulvic acid (35 ± 1.6) and the lowest in batch F3 without permeation enhancer i.e. fulvic acid (21 ± 1.3) as shown in Figure 4a and Figure 4b.

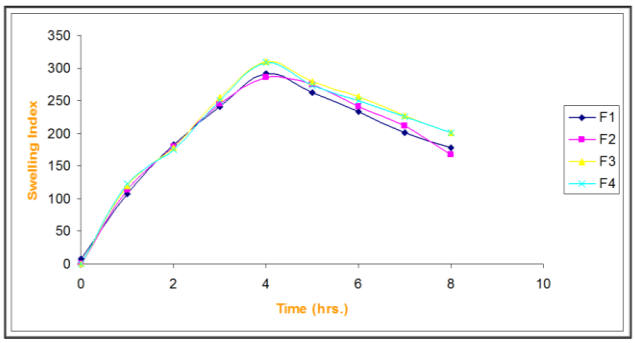

Figure 4a.Swelling index study of sustained release tablets without permeation enhancer of batches F1 to F4

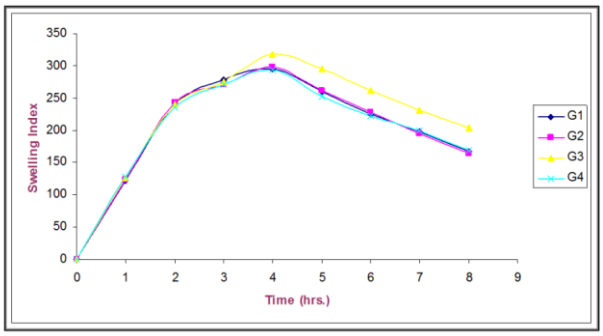

Figure 4b. Swelling index study of sustained release tablets with permeation enhancer of batches G1 to G4

The ex-vivo mucoadhesive 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[17]. Formulation G3 showed good mucoadhesive strength (28.8 ± 3.0).

The mucoadhesive time on buccal mucosa ranged from 7 to 16 hours as shown in Table 2.

Table 2-*In-vitro* Mucoadhesive study of Buccal Tablets of sumatriptan succinate

Batch Code	Ex- vivo Mucoadhesion Time (hrs)	Mucoadhesive Strength (gram)
F1	7 ± 0.3	11.7 ± 3.3
F2	8 ± 0.5	13.3 ± 2.1
F3	10 ± 0.7	26.8 ± 2.7
F4	12 ± 1.0	18.4 ± 2.4
G1	14 ± 1.2	20.6 ± 2.1
G2	13 ± 1.3	24.6 ± 2.4
G3	16 ±0.9	28.8 ± 3.0
G4	13 ± 1.1	25.4 ± 2.8

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-F4 & G1-G4) remain intact during the 12- hour period. *In-vitro* drug release study with out and with permeation enhancer is as shown in Figure 5a and Figure 5b.

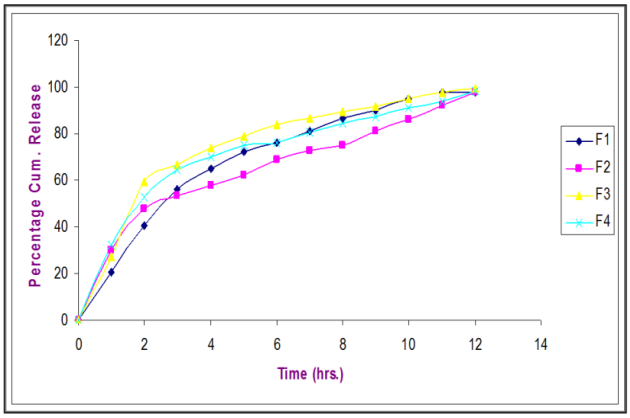

Figure 5a: Dissolution study of sumatriptan succinate mucoadhesive tablets without permeation enhancer in 6.8 pH buffer

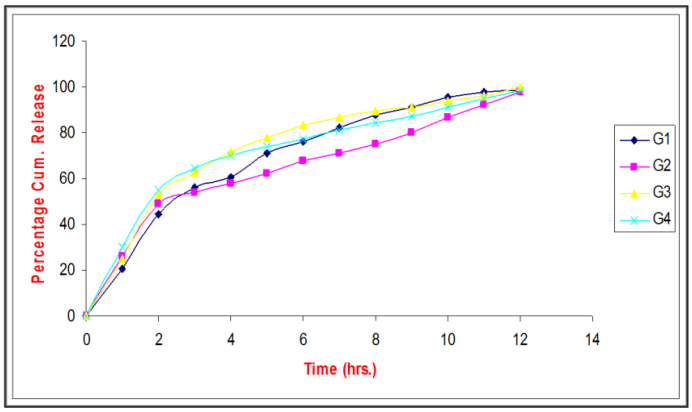

Figure 5b:- Dissolution study of sumatriptan succinate mucoadhesive tablets with permeation enhancer in 6.8 pH buffer

Permeation Study across Buccal Mucosa

The permeation study of buccoadhesive system was carried out using sheep buccal mucosa. The permeation study was carried out for system with and without permeation enhancer. Formulation G3 was subjected to an *in-vitro* buccal permeation study using a diffusion cell (Figure. 3c). The results showed drug permeation of 93.34±1.5 in 12 hours.

The permeation rate profile for the optimized formulation G3 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}.

The results of permeation studies are as shown in Figure 6.

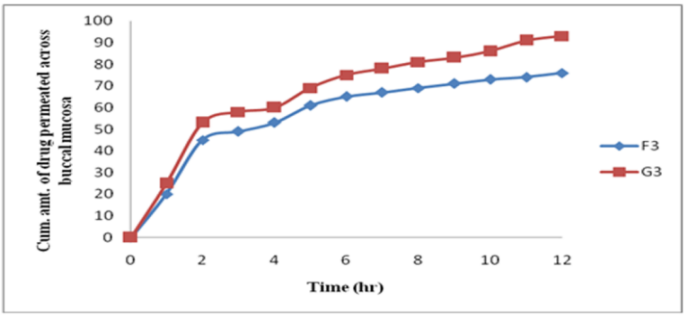

Figure 6:-Permeation study of optimized batches of sustained release tablets in 6.8 pH buffer

For all the batches, the values of n ranged from 0.5032 to 0.7034 (Table 3), indicating non-fickian release. Formulation G3 was optimized based on the *in-vitro* drug release (99.88±1.7 at. 12 hours), swelling index (35 ± 1.6at 8 hours) and ex vivo mucoadhesion strength (28.8 ± 3.0 gm) it showed good drug release with sufficient mucoadhesion

Table 3-Kinetics data of sustained release tablet in 6.8 pH buffer

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
G1	0.8374	0.9892	0.9735	0.9976	0.93
G2	0.7972	0.9762	0.9672	0.9842	0.89
G3	0.7667	0.9927	0.9725	0.9776	0.79
G4	0.7641	0.9725	0.9730	0.9886	0.88

CONCLUSION

Buccoadhesive tablets of sumatriptan succinate using fulvic acid as a permeation enhancer 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 from 75.30 to 93.34% across buccal mucosa. The in-vitro mucosal permeation has shown significant enhancement in permeation of sumatriptan succinate using fulvic acid in comparison with plain sumatriptan succinate tablet.

REFRENCES

1. Gavini E, Sanna J. Mucoadhesive vaginal tablets as veterinary delivery system for the controlled release of an antimicrobial drug. Acriflavin. AAPS Pharm SciTech 2002; 3:20.

2. Harris D. Drug Delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992; 81:1-10.
3. Parodi B. Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride. Drug Dev Ind Pharm 1996; 22:445-450.
4. Nagai T. Buccal/gingival drug delivery systems. J Control Release 1987; 6: 353-360.
5. Collin Dollery. Therapeutic Drugs 2 nd ed. vol- II. New York: Churchill Livingstone; 1999: S151-S154.
6. Ghosal S. Shilajit: Its origin and significance. Indian J. Indg. Med 1992; 9: 1-4.
7. Chopra RN. Chopra's Indigenous Drugs of India. Pub. By Dhu and Sons. Pvt. Ltd. Calcutta 1958:496, 560.
8. Agrawal SP. Enhancement of the dissolution rate of Ketoconazole through a novel complexation with fulvic acid extracted from shilajit. Asian J. Chem. 2008; 20 (2): 879-888.
9. Ghosal S, Lai J., Singh SK., Dasgupta G, Bhaduri J, Mukhopadhyay M, Bhattacharya SK. Phytother. Res. 1989; 3, 249.
10. Agrawal SP, Aquil M, Anwer MK, Asian J Chemistry 2007; 19:4711.
11. Agrawal SP. Enhancement of the dissolution rate of Ketoconazole through a novel complexation with fulvic acid extracted from shilajit. Asian J. Chem. 2008; 20 (2): 879-888.
12. Ansel HC. A Textbook of Pharmaceutical Dosage Form and Drug Delivery System. 8 th ed. B. I. Publication; 2005: 231, 234-238.
13. Lachman Leon and Lieberman HA. The Theory and Practice of Industrial Pharmacy. 4 th ed. Bombay: Varghese Publication House; 1991: 296-302,317,333.
14. Bottenberg P. Development and testing of bioadhesive fluoride containing slow- release tablets for oral use. J Pharm Pharmacol 1991; 43: 679-684.
15. Patel VM. Formulation, Evaluation and Comparison of bilayered and multilayered buccal devices of Propranolol hydrochloride. AAPS 2007; 8 (1):E1- E8.
16. Parodi B. Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride. Drug Dev Ind Pharm 1996; 22:445-450.
17. Gupta A. Measurement of bioadhesive strength of mucoadhesive buccal tablets: design of an in-vitro assembly. Indian Drugs 1992; 13: 361-365.
18. Patel VM. Formulation, Evaluation and Comparison of bilayered and multilayered buccal devices of Propranolol hydrochloride. AAPS 2007; 8 (1):E1- E8.

19. Ilango R. *In- vitro* studies on buccal strips of Glibencamide using chitosan. Indian J Pharm. Sci 1997; 59: 232-235.
20. Agarwal V. Design, development and biopharmaceutical properties of buccoadhesive compacts of Omeprazole. Drug Dev Ind Pharm 1999; 25: 701-709.