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Enhancement of oral bioavailabity of sumatriptan mucoadhesive buccal tablets using various polymers

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ABSTRACT

Buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. By the way improvisation of oral bioavailability of low bioavailability drugs can be achieved. Hence, in the present work mucoadhesive buccal tablets of Sumatriptan succinate will be prepared using different natural and synthetic polymers to improve the oral bioavailability. Buccal sustained release matrix tablets of Sumatriptan succinate containing different grades of HPMC were subjected to *in vitro* drug release studies in pH 6.8 Buffer for 8 hours. The cumulative percent of drug released from the formulations F7and F8 at the end of 8 hrs is 93.45±0.52, 97.04±0.7 respectively. Thus the formulation of aforementioned depicts that the bioavailability of the drug has been notably increased.

Keywords: Oral bioavailability, buccal tablets, Sumatriptan succinate and polymers.

INTRODUCTION

The popularity of oral route is attributed to patient acceptance, ease of administration accurate dosing, cost effective manufacturing methods, and generally improve the shelf life of the product In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drugs can be absorbed from the oral cavity through the oral mucosa either sublingually or buccally [1-5]. Absorption of therapeutic agents from these routes overcomes premature drug degradation within the gastrointestinal tract as well as active drug loss due to first-pass hepatic metabolism that may be associated with oral route of administration. Difficulties associated with the

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parental delivery and poor oral bioavailability provided the impetus for exploring alternative routes for the delivery of such drugs [6-10].

Buccal dosage forms can also be classified as either a reservoir or matrix type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug's release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction [11-15].

MATERIALS AND METHODS

All the chemicals and reagents used in the research work are obtained from the reputed vendors. Sumatriptan succinate is obtained as a gift sample from Dr. Reddys Laboratories Ltd., All others excipients are obtained from SD fine Chem [16-20].

Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Main objective of performing preformulation studies to generate useful information to prepare the formulation in developing stable and bioavailable dosage forms.

Drug and excipient compatibility studies

A successful formulation of a stable and effective solid dosage form depends on careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and not been used in formulation containing the active substance, the compatibility studies are of paramount importance.

Sumatriptan succinate stock solution

Standard stock solution was prepared by dissolving 10 mg of Sumatriptan succinate in 100 mL organic solvent of methanol to get concentration of 100 µg/mL solution [21-24].

Table 1. Master Formula (F1 to F6)

Ingredients	F1	F2	F3	F4	F5	F6
Drug(mg)	25	25	25	25	25	25
SLS(%)	0.05	0.05	0.05	0.05	0.1	0.2
Talc	0.7	0.7	0.7	0.7	0..65	0.55
Mg stearate	0.35	0.35	0.35	0.35	0.35	0.35
Crbopol 934P	12.5	25	37.5	12.5	12.5	12.5
HPMC K4M	-	-	-	12.5	12.5	12.5
HPMC K15M	-	-	-	-	-	-
HPMC K100M	-	-	-	-	-	-
MCC	31.4	18.9	6.4	18.9	18.9	18.9
Total weight(mg)	70	70	70	70	70	70

Table 2. Master Formula (F7 to F12)

Ingredients	F7	F8	F9	F10	F11	F12
Drug	25	25	25	25	25	25
SLS (%)	0.05	0.1	0.2	0.05	0.1	0.2
Talc	0.7	0..65	0.55	0.7	0..65	0..55
Mg stearate	0.35	0.35	0.35	0.35	0.35	0.35
Carbopol 934P	12.5	12.5	12.5	12.5	12.5	12.5
HPMC K4M	-	-	-	-	-	-
HPMC K15M	12.5	12.5	12.5	-	-	-
HPMC K100M	-	-	-	12.5	12.5	12.5
MCC	18.9	18.9	18.9	18.9	18.9	18.9
Total weight(mg)	70	70	70	70	70	70

FTIR Compatibility Studies

FTIR spectra of pure drug and formulation with other ingredients were recorded**.** The FTIR Spectra of pure Sumatriptan succinate drug and polymer was compared with the FT-IR spectrum of drug and polymer, physical mixture (Sumatriptan succinate, HPMC K15 and Carbopol) in the figures, respectively. The characteristic functional groups of the pure Sumatriptan succinate showed the peaks at the following wave number region. NH stretching (Amine) at 3369.04 cm-1, Ketone (C=O) stretching at 1707.11 cm^{-1}, C-N at 1392.79 cm^{-1}, S=O at 1079.81 cm^{-1}.

Table 3. FTIR peaks of drug and excipients

IR Spectra	Peak of functional groups [Wave number (cm^{-1})]					
	NH	**CH**	**C=O**	**C-N**	**S=O**	**C=C**
Sumatriptan succinate	3369.04	2970.48	1707.11	1392.79	1079.81	1542.65
Glimepride+ Carbopol 934P	3369.06	2931.30	1724.28	1393.69	1080.01	1542.68
Sumatriptan succinate+ HPMC K15M	3369.09	2933.21	1708.32	1392.79	1079.51	1542.49
Optimized formulation	3369.06	2930.38	1708.32	1392.79	1079.5	1542.40

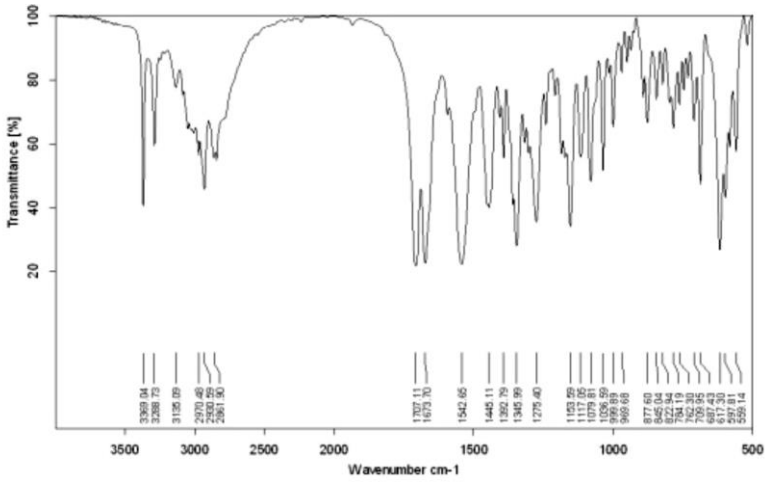

Figure 8. FTIR spectrum of pure drug.

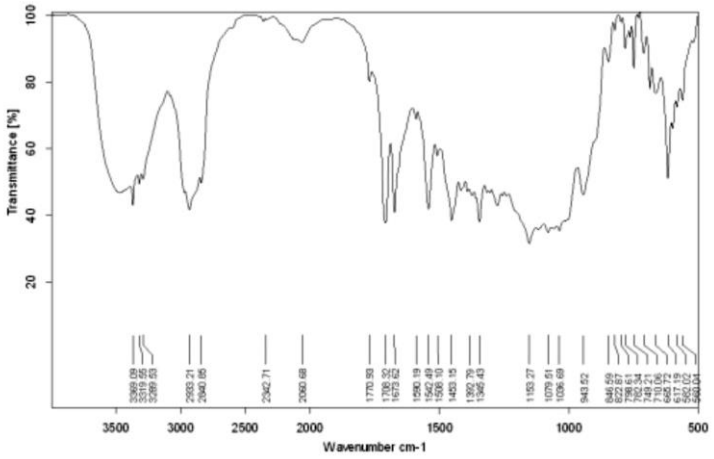

Figure 9. FTIR spectrum of drug and HPMC K15M

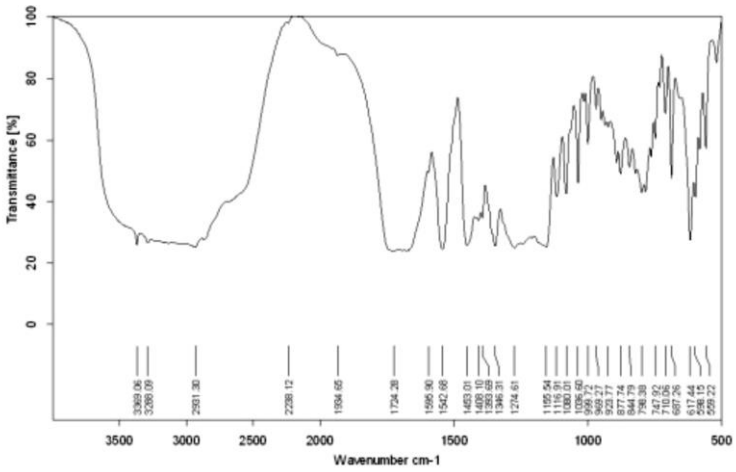

Figure 10. FTIR spectrum od Drug and Carbopol

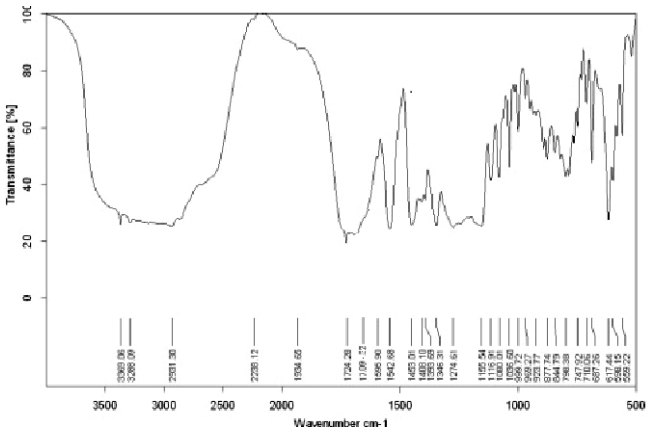

Figure 11. FTIR spectrum of final formulation.

Standard graph in phosphate buffer pH 6.8 (λ_{max} 249nm)

Standard graph of Sumatriptan succinate was plotted as per the procedure in experimental method. The standard graph of Sumatriptan succinate showed good linearity with R^2 of 0.996, which indicates that it obeys "Beer- Lamberts" law.

Table 19. Standard graph of Sumatriptan succinate in phosphate buffer pH 6.8

Concentration (µg/mL)	Absorbance
0	0
8	0.301
10	0.392
12	0.483
14	0.572
16	0.668
18	0.741

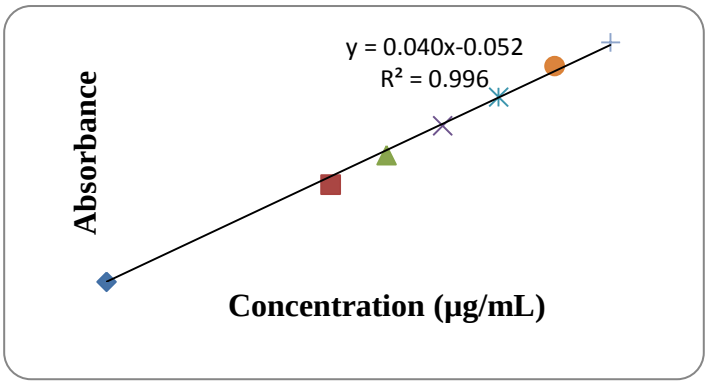

Figure.13 Standard graph of Sumatriptan succinate in phosphate buffer pH 6.8

Pre-compression parameters.

The pre-compression parameters like bulk density, angle of repose, tapped density. Carr's index and Hausner ratio have been performed.

Table 20. Pre-compression parameters.

S. NO	Angle of repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's Index (%)
F1	21.04±0.57	0.22±0.02	0.26±0.12	1.19± 0.06	16.34±0.02
F2	23.08±0.59	0.22±0.08	0.24±0.06	1.06±0.64	9.46±0.15
F3	21.36±0.38	0.23±0.07	0.25±0.015	1.07±0.34	6.08±0.45
F4	25.32±0.61	0.23±0.02	0.24±0.06	1.05±0.45	5.33±0.09
F5	24.45±0.12	0.23±0.07	0.27±0.03	1.16±0.12	13.82±0.52
F6	22.79±0.21	0.27±0.01	0.31±0.08	1.12±0.16	11.36±0.30
F7	23.92±0.69	0.26±0.01	0.29±0.12	1.10±0.78	9.62±0.10
F8	22.47±0.09	0.30±0.07	0.33±0.07	1.09±0.04	8.85±0.09
F9	25.69±0.71	0.35±0.65	0.38±0.14	1.21±0.06	17.39±0.03
F10	26.10±0.65	0.33±0.06	0.41±1.31	1.24±0.034	19.68±0.20
F11	21.38±0.08	0.29±0.09	0.34±0.09	1.18±0.08	15.31±0.09
F12	25.53±0.59	0.28±0.08	0.32±0.02	1.17±0.06	14.82±0.03

Physicochemical characterization of buccal tablets

The shape and size of the prepared tablets were found to be within the limit. The average weight was found to be within the prescribed limit. The hardness of the tablets was found to be in the range of 3.0±0.21 to 4.5±0.64 (kg/cm^2).

Table 21. Physico-chemical parameters of Sumatriptan succinate buccal tablets

Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness ($kg/cm^{2)}$	Friability (%)	Assay (%)
F1	69.28 ± 0.61	1.85 ± 0.03	4.5±0.25	0.55±0.07	98.05 ± 0.84
F2	70.04 ± 0.80	1.76 ± 0.02	4.0±0.30	0.63±0.13	99.73 ± 0.56
F3	70.38 ± 0.71	1.94 ± 0.03	3.0±0.45	0.66±0.08	97.15 ± 1.2
F4	71.45 ± 0.64	1.95 ± 0.02	3.5±0.20	0.58±0.19	99.77 ± 0.60
F5	69.91 ± 1.01	1.97 ± 0.02	3.5±0.28	0.64±0.16	101.96± 0.54
F6	69.98 ± 0.82	2.01 ± 0.01	3.5±0.40	0.47±0.17	99.81 ± 0.96
F7	70.38 ± 0.80	2.00 ± 0.02	3.0±0.21	0.66±1.2	97.86 ± 1.6
F8	68.04 ± 0.71	1.94 ± 0.03	4.5±0.64	0.65±0.65	100.81± 1.21
F9	69.94 ± 0.75	2.05 ± 0.02	4.0±0.29	0.43±0.09	99.35 ± 0.85
F10	68.68±1.2	2.06 ± 0.01	4.5±0.40	0.61±0.48	100.65± 0.96
F11	70.45 ± 0.64	2.04 ± 0.02	3.5±0.14	0.66±0.12	99.83 ± 0.52
F12	70.71 ± 1.01	2.55 ± 0.02	3.5±0.15	0.58±0.78	98.90 ± 0.75

Each value represents the mean ±SD (*n* =3)

In vitro drug release studies

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Sumatriptan succinate from different formulations.

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	47.9±0.8	37.8±0.65	35.77±1.1	45.7±1.1	41.06±2.5	37.9±1.5
1	61.07±0.6	48.06±2.1	47.34±0.75	66.1±1.5	55.68±0.9	51.68±0.9
2	90.9±1.32	81.43±1.45	71.5±2.6	74±2.3	73.3±1.6	64.7±0.5
3	-	94.72±0.96	88.92±0.45	91.6±1.7	84.8±1	81.73±1.5
4	-	-	97.19±0.96	96.65±0.9	92.6±0.7	88.96±0.3
5	-	-	-	-	98.04±0.9	91.09±1
6	-	-	-	-	-	98.45±2.1
7	-	-	-	-	-	-
8	-	-	-	-	-	-

Table

Time (hr)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
0.5	21.52±0.5	18.76±0.45	34.6±0.29	3.2±0.5	3.0±0.5	2.6±0.5
1	35.84±0.5	34.06±0.93	57.8±0.7	8.2±1	3.8±1	4.2±0.7
2	55.23±0.72	46.89±0.25	72.12±2.5	18.8±1.5	8.8±1.5	9.9±1.6
3	79.05±0.23	52.43±1.2	85.03±1.9	29.6±0.9	16.6±0.9	18.5±1.8
4	83.03±0.15	61.05±1.8	91.67±2.1	45.7±0.7	24.2±0.7	32.1±2.1
5	86.41±1.6	70.65±0.9	94.7±1.7	54.9±1.7	31.3±1.5	42±0.5
6	88.63±0.9	88.91±0.16	99.27±1.3	66.1±1.9	42.0±0.95	54.3±1.2
7	91.06±1.6	93.46±0.8	-	74.0±0.9	51.9±2.1	62.7±1.6
8	93.45±0.52	97.04±0.7	-	90.3±1.8	63.7±1.6	76.1±2.5

In vitro release of Sumatriptan succinate from Carbopol 934.

Formulations F1, F2 and F3 could not retarded drug release. In the formulation F1, F2, F3 only single polymer is used.

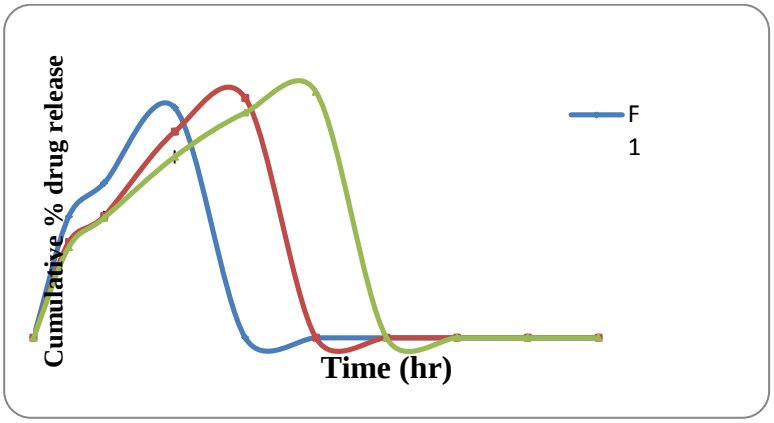

Figure14. *In vitro* release of Sumatriptan succinate from HPMC K4M.

In vitro release of Sumatriptan succinate from HPMC K4M and Carbopol

Buccal sustained release matrix tablets of Sumatriptan succinate containing HPMC K4 and Carbopol 934P were subjected to *in vitro* drug release studies in pH 6.8 Buffer for 8 hours.

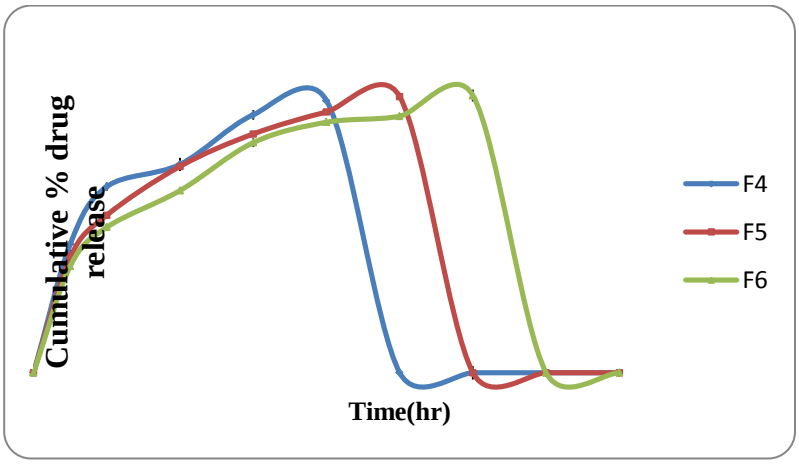

Figure 15. *In vitro* release of Sumatriptan succinate from HPMC K4M and Carbopol 934P

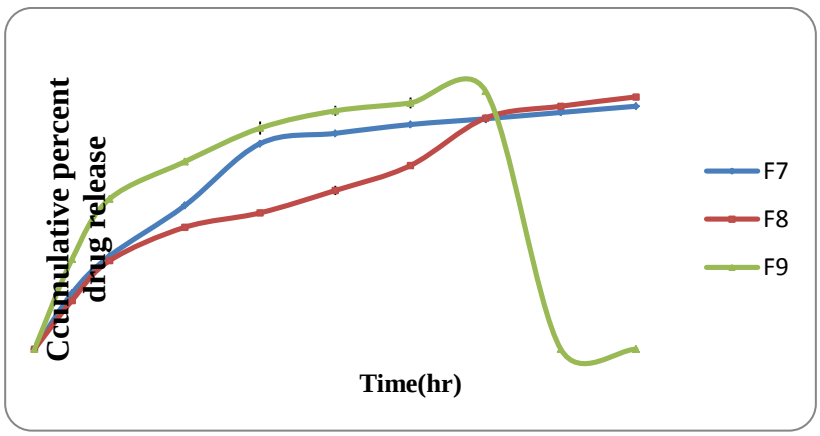

Figure 16. *In vitro* relies of Glimipiride form HPMC K15M and carbopol934P

In Vitro Release of Sumatriptan succinate from HPMC K100M and Carbopol

Formulations of Sumatriptan succinate containing HPMC K100M and Carbopol (F10, F11 and F12) showed the drug release of 90.3±1.8, 63.7±1.64 and 76.1±2.5 at the end of 8th hr respectively.

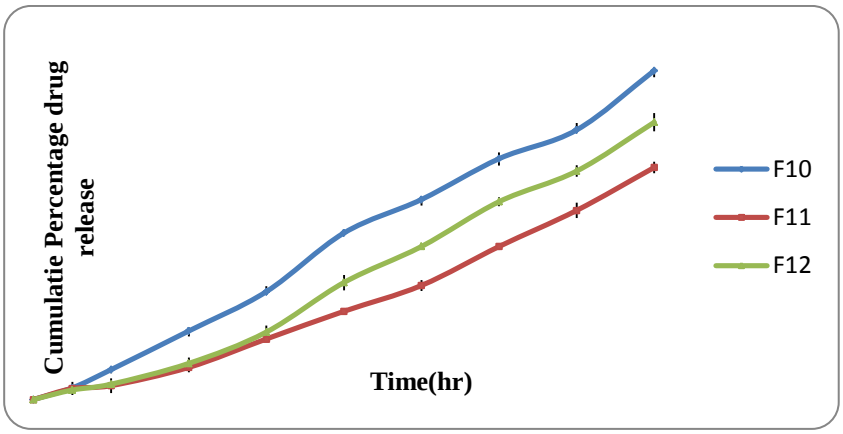

Figure 17. *In Vitro* Release of Sumatriptan succinate from HPMC K100M and Carbopol

Swelling Studies of buccal tablets

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drug and proper bioadhesion.

Table 24. Swelling studies of buccal tablets

Time (hrs)	% Swelling index
	F8
0	0
0.5	3.19± 0.39
1	6.50±0.11
2	9.28±0.28
3	12.15±0.31
4	13.44±0.32
5	15.35±0.71
6	17.64±0.19
7	19.35±0.30
8	20.82±0.63

Each value represents the mean ± SD (n=3)

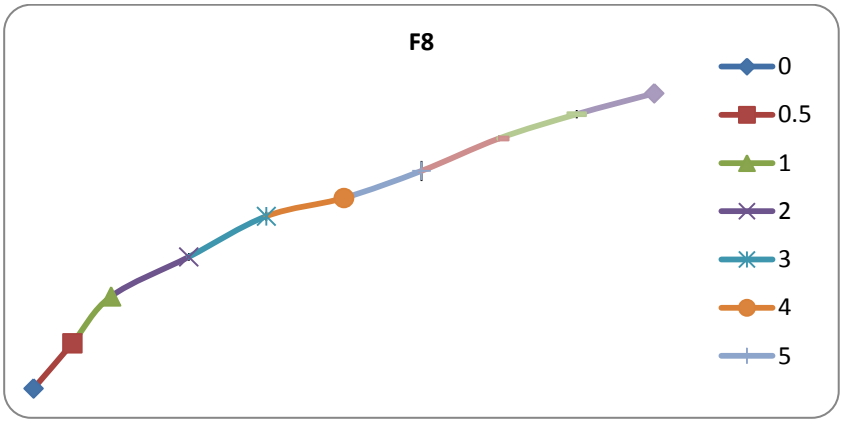

Figure 18. Swelling Studies of Sumatriptan succinate selected buccal tablets

Ex vivo permeation studies of Sumatriptan succinate buccal tablets

Based on the *in vitro* drug release studies, F7, F8 and F9 selected for the *ex vivo* permeation study. The flux, permeation coefficient and cumulative percent drug permeated from formulations F7, F8 and F9 were found to be 0.6029 $mg.hrs^{-1}cm^{-2}$, 0.0753cm/h and 58.4% respectively. Due to the low permeability of drug from the formulation, permeation enhancer (sodium taurocholate) was added in the concentration of 10 mM to the optimized formulation to increase the permeability.

Table Drug release of Sumatriptan succinate *Ex vivo* permeated buccal tablets

Time (hrs)	Drug solution	F7	F8	F9	Formulation without enhancer
0	0	0	**0**	0	0
0.5	12.74±0.13	11.30±0.19	**14.53±0.05**	16.23±0.05	10.53±0.91
1	28.23±0.17	23.64±0.34	**29.43±0.14**	31.33±0.14	19.97±0.56
2	30.24±0.21	37.74±0.85	**36.71±0.37**	37.47±0.37	34.68±0.85
3	38.62±0.15	47.61±0.45	**49.77±2.13**	53.65±2.13	43.26±1.02
4	46.72±0.16	54.22±2.09	**55.98±1.33**	55.28±1.33	51.70±2.49
5	57.81±0.23	61.43±1.06	**57.32±1.19**	58.24±1.19	56.89±1.90
6	68.54±0.53	67.31±0.72	**66.78±1.02**	64.81±1.02	62.40±1.30
7	78.13±0.89	78.77±1.23	**77.99±2.19**	76.69±2.19	71.13±0.72
8	87.29±1.32	81.33±1.89	**85.28±3.43**	83.28±3.43	78.34±1.36
FLUX	110.452 $\mu g.hr^{-1}cm^{-2}$	189.87µg/hr cm^2	**194.15µg/hr cm^2**	193.45µg/hr cm^2	168.96 µg/hr cm^2

Each value represents the mean ± SD (n=3)

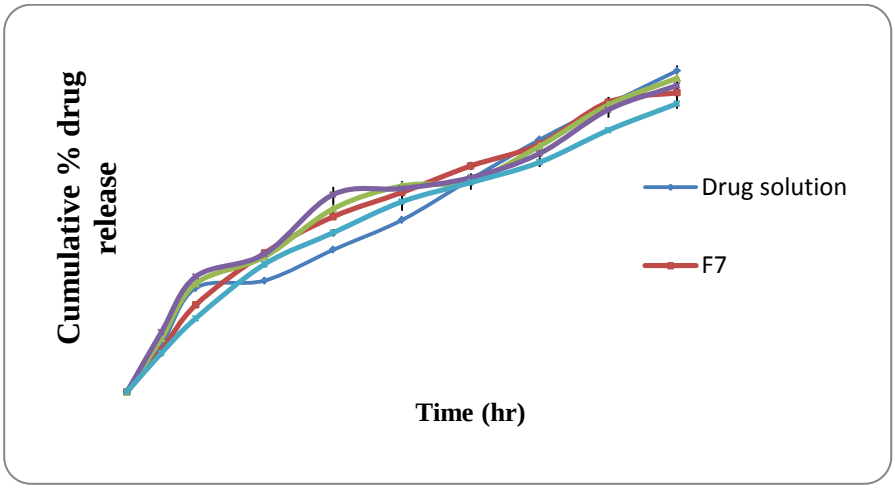

Figure19. Drug release of Sumatriptan succinate *Ex vivo* permeated buccal tablets.

The *ex vivo* permeation studies of selected formulations were conducted, the values of flux and permeability coefficients were found to be 189.87µg hr^{-1} cm^2, 193.45µg hr^{-1} cm^2, 194.15µg hr^{-1} cm^2 and 0.158 cm/h, 0.126 cm/h and 0.197 cm/h.

CONCLUSION

Current research revealing of the fabrication of Sumatriptan succinate for the betterment of the oral bioavailability with various synthetic and natural polymers has given, a considerable attention and significance towards the results. The formulation F8 has shown remarkable results in the aspect of post and pre compressional parameters with the drug release of more than 85 % in 8 hours, it is quite satisfactory. Hence it

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