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Formulation and evaluation of simvastatin buccal adhesive tablets

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ABSTRACT

The objective of the study was to develop buccal adhesive tablets of Simvastatin using mucoadhesive polymers. Simvastatin has short biological half-life (3hr), high first-pass metabolism and poor oral bioavailability (5%), hence an ideal candidate for buccal delivery system. The tablets were prepared by direct compression technique using xanthan gum, guar gum, chitosan and aloe gum. Aloe gum was extracted from *Aloe Barbadensis miller* leaves. Formulations were evaluated for weight variation, hardness, friability, drug content, swelling studies, determination of mucoadhesive strength and in vitro release studies. FTIR studies show no evidence on interaction between drug, polymers and other excipients. *In vitro* drug release studies revealed that release of Simvastatin from different formulations varies with characteristics and composition of polymers. Formulation F3 selected as optimized formulation based on physicochemical parameters, and in vitro release rates and follows zero order drug release. Chitosan and guar gum were helpful for controlling the drug release in better way when used in proper combinations. The results indicate that suitable bioadhesive buccal tablets for Simvastatin with controlled drug delivery could be prepared.

Keywords: Simvastatin, buccal delivery system, xanthan gum, guar gum,chitosan

INTRODUCTION

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal, etc. Thus mucoadhesion may be defined as drug delivery systems that utilize property of bioadhesion of certain water-soluble polymers that become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. This system of drug delivery is called mucoadhesive drug delivery system. The buccal region of oral cavity is an attractive target for administration of drug of choice. Buccal drug delivery involves the administration of desired drug through the buccal mucosal lining of the oral cavity. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. It is also possible to administer drugs to patients who unconscious and less co-operative. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with

various combinations of polymers, absorption enhancers.[1][2]

Simvastatin is HMG Co - A reductase inhibitors widely used in the treatment of hyperlipidemias and cardiovascular diseases and it is known to have low oral bioavailability (5%) due to an extensive high first-pass effect and its availability in less dose size i.e., in few mg. Hence, it is suitable candidate for buccal drug delivery. The aim of the present study was to design and develop buccal adhesive tablets of Simvastatin that could be applied to the buccal mucosa to release the drug unidirectionally in buccal cavity in order to decrease gastric irritation and avoid first pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.[3]

MATERIALS AND METHODS

Materials: Simvastatin was gift sample from Biocon Bangalore, Xanthan Gum and Microcrystalline Cellulose was obtained from Research Lab Fine Chem Industries, Mumbai, Guar Gum from Himedia Laboratories (P) Ltd, Mumbai and Chitosan was obtained from Indian Sea Foods, Cochin.

Preformulation studies:

Determination of melting point of Simvastatin

Drug–excipient compatibility studies

Drug–polymer compatibility studies: FT-IR spectroscopy was employed to ascertain the compatibility between Simvastatin and the selected polymers. The pure drug , polymers, drug with excipient and final formulation were scanned separately.

Extraction of Aloe mucilage: The fresh leaves of *Aloe barbadensis Miller* were collected and washed with water to remove dirt and debris. Incisions were made on the leaves and left overnight. The leaves were crushed and soaked in water for 5–6 hours, boiled for 30 minutes and left to stand for 1 hour to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 45°C, collected, grounded, passed through a # 80 sieve and stored in desiccators at 30°C and 45% relative humidity before use.[4]

Preparation of buccal tablets: Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. The ingredients were mixed and blended for 10 minutes in an inflated polyethylene pouch. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. Powder blend were directly compressed using 10.05 mm, round-shaped flat punch in a single station tablet compression machine.[4]

Evaluation of Powder Blend [5][6]

Angle of repose : The angle of repose was determined by the fixed funnel and free standing cone method . A funnel with the end of the stem cut perpendicular to its axis was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The powder mixture was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius (r) of the base of the pile was determined and the tangent angle of repose was calculated by,

The angle θ as defined by the equation,

$\tan(\theta) = h/r$

Where, h = Powder bed height

d = Powder bed diameter

Bulk density: Bulk density is defined as a mass of a powder divided by the bulk volume. The power sample under test was screened through sieve no. 18 and the sample equivalent to 25 gm was weighed and filled in a 100 ml graduated cylinder and the powder was levelled and the unsettled volume, V_o was noted.

The bulk density was calculated in g/cm^3 by the formula.

Bulk density = M/V_o

M = Powder mass

V_o = Apparent unstirred volume

Tapped density: The powder sample under test was screened through sieve no.18 and the weight of sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder was carried out manually 50 times initially and the tapped volume V_o was noted. Tapping was proceeding further for an additional tapping 10 times and tapped volume, V_b was noted. The difference between two tapping

volume was less the 2%, V_b was considered as a tapped volume V_t.
The tapped density was calculated in g/cm^3 by the formula,
Tapped density = M/V_t ,M =weight of sample power taken
V_t =tapped volume

Compressibility index: This property is also known as Carr's consolidation index. It directly related to the relative flow rate, cohesiveness and particle size. The bulk density, tapped density was measured and compressibility index was calculated using formula,

$$\text{Consolidation index} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \times 100$$

***Hausner ratio*[7]:** Hausner ratio of the blend was calculated using the following formula,

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

***Evaluation of tablets* [2][6]**

General appearance and organoleptic properties
The colour of a product must be uniform within a single tablet, from tablet to tablet and from lot to lot. Twenty tablets of each formulation were taken to check any discoloration or surface roughness in the tablet formulation.

Size and shape of tablets: The size and shape of tablet can be dimensionally described, monitored and controlled. A compressed tablets shape and dimensions are determined by the tooling during the compression process. The thickness of a tablet is the only dimensional variable related to the process. The physical dimension of the tablet, along with the density of the materials in the tablet formulation and their proportions, determine the weight of the tablet.

Weight variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if no more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in and none deviate by more than twice the percentage shown and the test was carried out according to USP.

Friability: The friability was measured using Roche friabilator. Twenty tablets from each batch were ($W_{initial}$) accurately weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes (100 revolutions). After revolutions the tablets were dusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{(\text{Initial weight of tablets} - \text{Final weight of tablets})}{\text{Initial weight of tablets}} \times 100$$

Hardness test: Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Thickness: The thickness of the tablets was measured by vernier calipers. Five tablets were used and the average value was calculated and expressed in mm.

***Determination of drug content* [3]:** Ten tablets were taken and powdered; powder equivalent to one tablet was weighed accurately and allowed to dissolve in 10 ml Dimethyl sulphoxide and make up to 100 ml with distilled water on a rotary shaker overnight. After filtration through whatmann filter paper and sufficient dilution with distilled water, samples were analyzed spectrophotometrically at 238 nm. This procedure was repeated thrice. Amount of drug present was determined from the standard curve of Simvastatin.

***Swelling Index*[8]:** The swelling index of the buccal tablet was evaluated by using pH. 6.8 phosphate buffer. The initial weight of the tablet was determined (w_1). The tablet was placed in pH. 6.8 phosphate buffer (6 ml) in a petri-dish placed in an incubator at 37±1°C and tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, to 9.0 h), and re-weighed (w_2) . The swelling index was calculated using the formula:
Swelling Index = [(W2-W1) ÷ W1] × 100

Where, W1 = initial weight of the tablet

W2 = final weight of the tablet.

***In vitro drug release of buccal tablets*[9]:** The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus.

The dissolution medium consisted of phosphate buffer pH 7.0 containing 0.5 % dodecyl sodium sulfate in 0.01 M sodium phosphate;900 ml. The release was performed at $37^oC \pm 0.5^0C$, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 239 nm.

Ex vivo bioadhesion strength measurement (mucoadhesive strength) **[10]:** Bioadhesive strength was assessed in terms of the weight in grams required to detach the tablet from the membrane.

Fabrication of the test assembly: The working of a double beam physical balance formed the basis of the bioadhesion test apparatus fabricated. The left pan was removed and hung with a stainless steel chain. A stainless steel block was hung with the chain to balance the weight of the other pan. The height of total set up was adjusted to accommodate a glass container of 4.2 cm diameter and 4.2 cm height below it, leaving headspace of about 0.5 cm in between. Another stainless steel block (2) was kept inside the glass container. Suitable weights were added (15.0 gm) on the right pan to balance.

Measurement of adhesive force: Two sides of the balance were balanced with a 15.0 gm weight on the right hand side. The goat buccal mucosal membrane, excised and washed, was attached with the mucosal side upward over the stainless steel block (2). It was then placed into the glass container, which was then filled with 6.8 phosphate buffer, such that the 6.8 buffer reaches the surface of the mucosal membrane and keeps it moist. This was then kept below the left-hand side of the balance, the tablet was then stuck with little moisture to the stainless steel block 1 hanging on the left-hand side and the beam is raised with a 15.0 gm weight on the right pan removed. This lowers the stainless steel block 1 along with the tablet over the mucosa with a weight of 15.0 gms. The balance was kept in this position for 3 min and then slowly weights were added on the right pan till the tablet separated from the mucosal surface. The excess weight on the pan (i.e., the total weights minus 15.0 gm) is the force required to separate the tablet from the mucosa. The bioadhesive strength of the tablet is represented in grams. Three tablets were tested from each batch. After each measurement the tissue was gently and thoroughly washed with saline and left for 5 min before the next measurement. Fresh tissue was used for each batch of tablets.

Tablet surface pH evaluation **[3]:** The surface pH of the tablets was determined in order to investigate the possibility of any side effect, in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was our attempt to keep surface pH as close to neutral as possible. The tablet is allowed to swell by keeping it in contact with 1 ml of phosphate buffer pH 6.8 for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing equilibrating for 1 min. Thereafter surface pH measurements were recorded.

Kinetic modelling of in vitro drug release: The data obtained from in vitro release studies of various batches of tablets were fitted to various models such as zero order, first order, higuchi and korsmeyer peppas to obtain the kinetic modelling of drug release.

To study the release kinetics the data obtained from *in vitro* drug release studies were plotted in various kinetic models.

1. Zero order rate kinetics : Cumulative percentage of drug release v_s time.
2. First order rate kinetics : Log cumulative % of drug remaining v_s time.
3. Higuchi model : Cumulative percentage of drug released v_s square root of time.
4. Korsmeyer Peppas model: Log cumulative % of drug release v_s log time.

The plots were drawn using graph pad prism version 5 and the regression equations were obtained for each plot. The correlation coefficient value (r^2) of the plot was obtained. The model with the highest correlation coefficient value (r^2approches unity) was chosen as the best fit kinetic model.

Zero order kinetics

A zero order release can be predicted by using the equation:

$$\mathbf{Q_t = Q_o - K_o t}$$

Where,

Q_0 = initial amount of drug present in solution (most cases Q_0=0)

Q_t = the amount of drug release at time t.
K_0 = the zero order release rate constant.

A graph of cumulative percentage of drug release vs time yields a straight line with a slope equals to K_0.

First order kinetics

The first kinetics describes the release from a system where the release rate is concentration dependent. It can be described by the following equation:

$$\ln Q = \ln Q_o - K_1 t$$

Where, K_1 = first order release constant.

Higuchi model kinetics

The drug release can be predicted by the following equation:

$$Q = Kt^{1/2}$$

Where, K is Higuchi dissolution constant.
t is the time in hrs
The model predicts that the drug release from the dosage form is directly propotional to the square root of time.

Korsmeyer Peppas model

To evaluate drug release mechanism of drug, the *in-vitro* release data was plotted in korsmeyer equation as log cumulative percentage of drug release vs log time and exponent *n* was calculated through slope of the straight line.

Korsmeyer equation as follows:

$$Mt/M^{\alpha} = Kt^n$$

Where, M_t/M_α is the fractional solute release
t = the release time ;
k = the kinetic constant

n is an exponent which indicates the mechanism of drug release. In the present study the limits considered were *n*= 0.45 indicates a classical Fickian diffusion- controlled release and n=0.89 indicates a case II relaxation release transport; non-fickian, zero order release value of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport. After the value reaches 0.89 and above the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order.

RESULTS AND DISCUSSION

Mucoadhesive buccal tablets were prepared by adding different concentrations of mucoadhesive polymers and by direct compression method. The characterization of mixed blend was carried out for all formulations. The bulk density of mixed blend varied between 0.5348-0.6702 gm/cm$^{3.}$ Tapped density were found in the range of 0.7213 to 0.7821g/cm^3. Hausner's ratio less than 1.39. Compressibility index was found between 9.00 to 21.27% indicates better flow. Angle of repose was found between 27.04 to 34.56^0. The tablets were prepared & characterized. The weight of the tablet of all formulations was found to be 248mg to 253 mg. Friability were found to be 0.39-0.58 % and hardness was found Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with rate of hydration. Maximum swelling was seen with formulations F1, F2, and F3 containing polymers Xanthan gum, guar gum and aloe-gum combinations. Tablets of all formulations had shown a surface pH values in the range of 6.01-6.50 that indicates no risk of mucosal damage or irritation.

In vitro drug release studies revealed that release of Simvastatin from different formulations varies with characteristics and composition of polymers. The release rate decreased with increasing concentration of xanthan gum. Formulation F3 showed relatively high rate of release of drug which is due to rapid swelling and erosion of Guar gum. Chitosan and guar gum were helpful for controlling the drug release in better way when used in proper combinations.

The bioadhesion characteristics were found to be affected by the nature and proportions of bioadhesive polymers used. The strength of muccoadhesive bond was observed with formulation F3 containing guar gum and Aloe-gum, and chitosan was found to be 13 and F7 as 8. From the above results better four formulations were subjected to kinetic drug release studies. From this the formulation F3 was best fitted into Zero order kinetic. The drug release was dominated by the erosion and swelling of the polymer. From the release exponent in the korsmeyer-peppas model it could be suggested that the mechanism that leads to the release of drug was non -fickian diffusion.

CONCLUSION

Overall evaluations of the mucoadhesive behaviour of tablets show good bioadhesive properties and are suitable for transmucosal applications with proper release rates.The present study conclusively proved that Simvastatin buccal

adhesive tablets could be successfully developed using various natural polymers. The prepared tablets gave promising results with respect to mucoadhesion strength and *in vitro* release from the dosage form.

ACKNOWLEDGEMENTS

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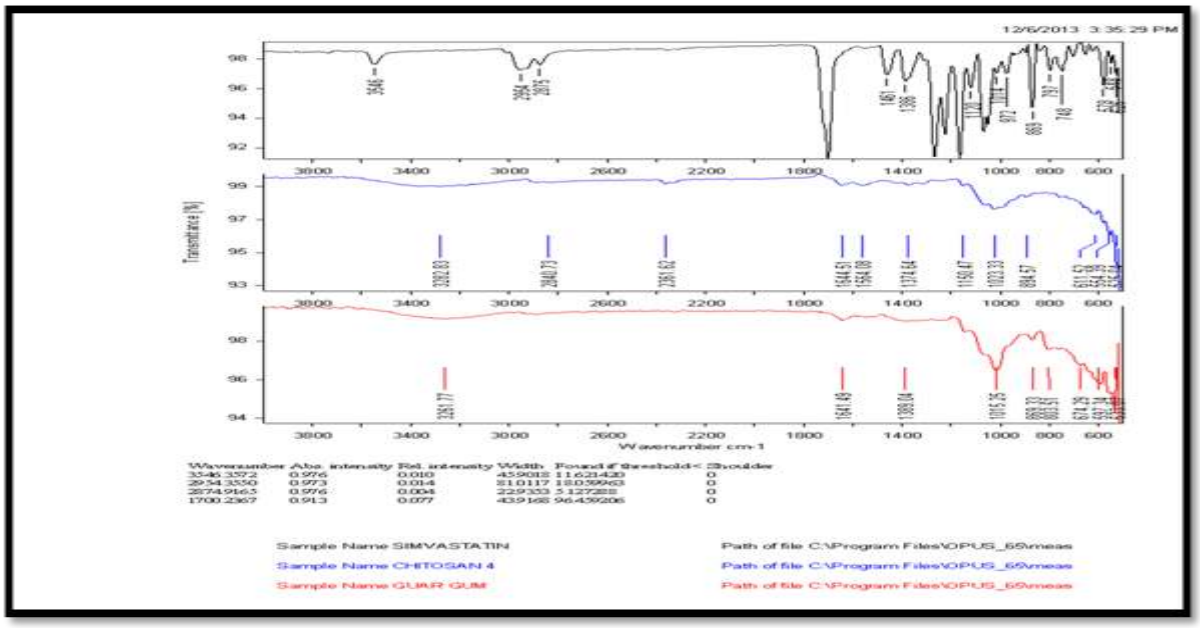

Figure: 1 FTIR Spectra of Simvastatin, Chitosan and Guar gum

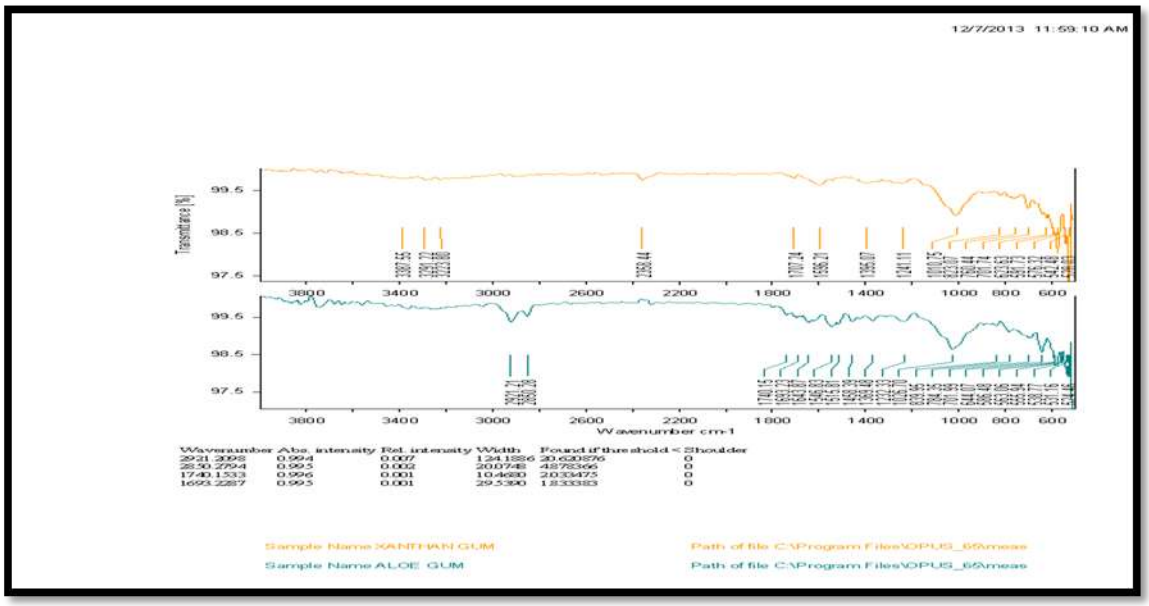

Figure: 2 . FTIR Spectra of Xanthan Gum ,Aloe Gum

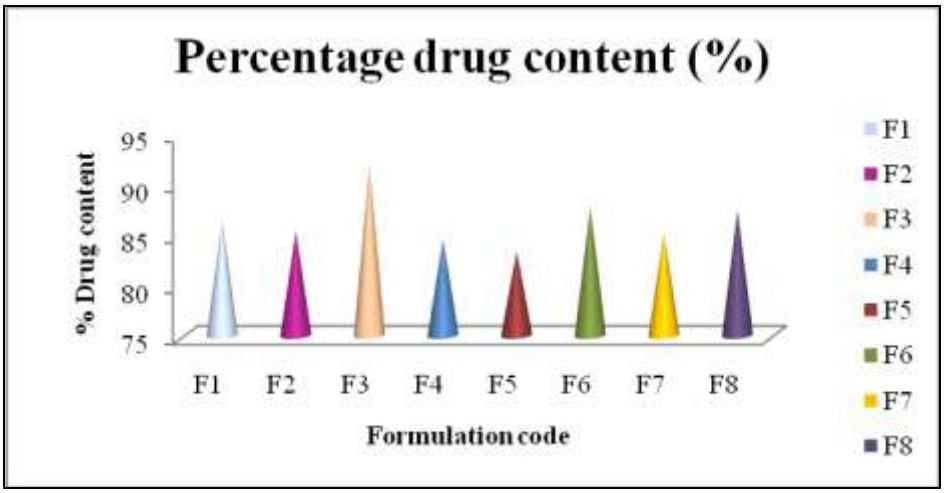

Figure: 3 Drug content determination

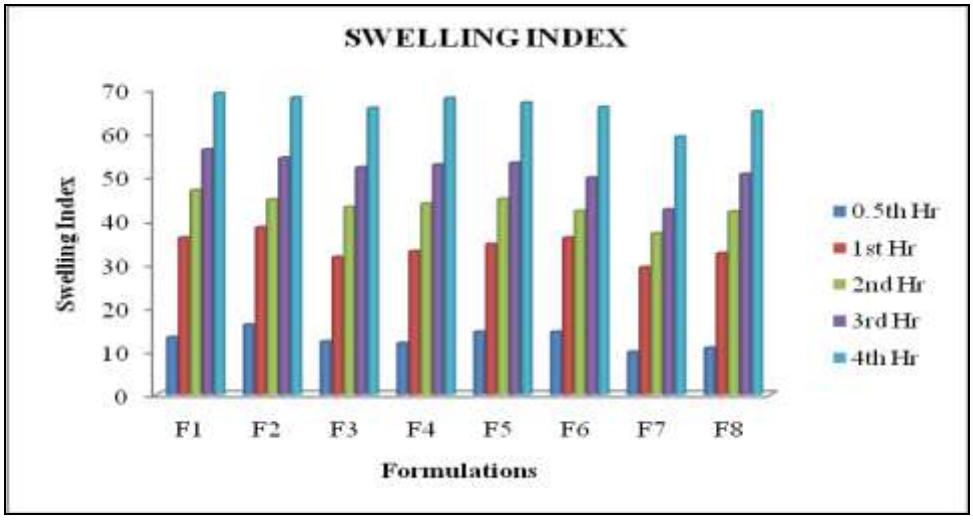

Figure : 4 Swelling index of various formulations

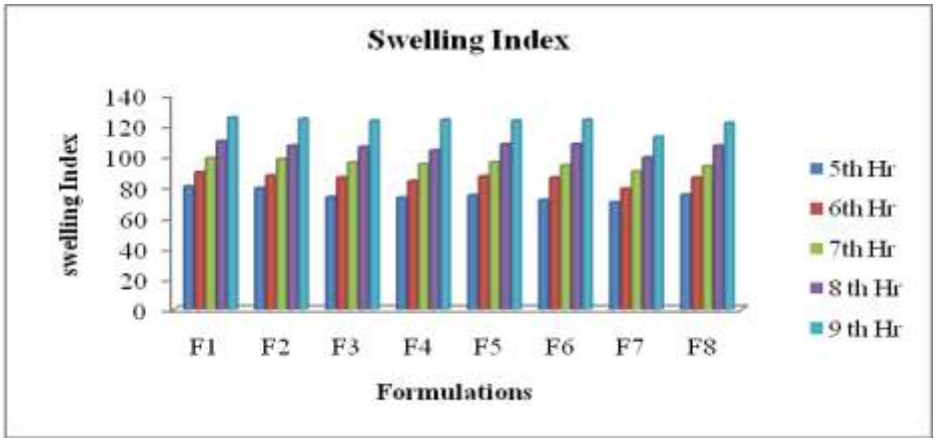

Figure : 5 Swelling index of various formulations

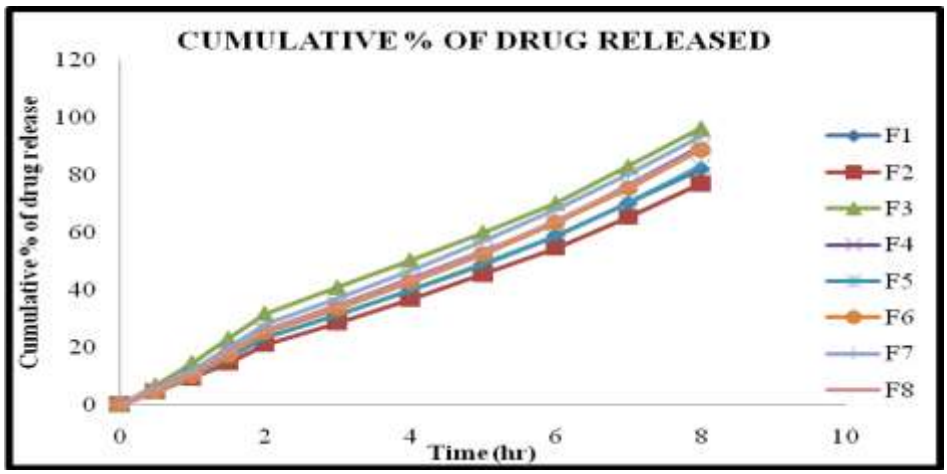

Figure: 6 Cumulative % of drug release

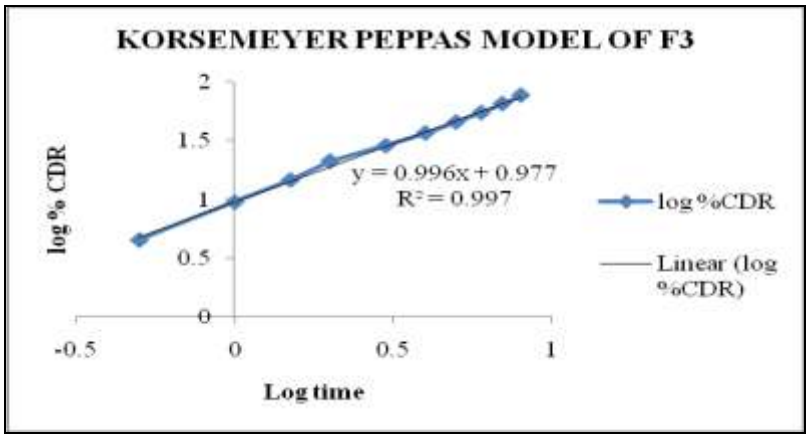

Figure : 7

Figure : 8 Modified physical balance for the determination of mucoadhesive strength

Table :1: Composition of buccal adhesive tablets of Simvastatin (for 1 tablet)

	F1	F2	F3	F4	F5	F6	F7	F8
Simvastatin(mg)	10	10	10	10	10	10	10	10
Aloe (mg)	8	8	8	8	8	8	8	_
Xanthan gum(mg)	20	30	_	30	60	_	_	_
Guar gum (mg)	20	30	30	_	_	60	_	30
Chitosan (mg)	20	_	30	30	_	_	60	30
M.C.C (mg)	80	80	80	80	80	80	80	80
Menthol (mg)	1	1	1	1	1	1	1	1
Magnesium stearate (mg)	3	3	3	3	3	3	3	3
Talc(mg)	1	1	1	1	1	1	1	1
Lactose (mg)	80	80	80	80	80	80	80	88
Ascorbic acid (mg)	3	3	3	3	3	3	3	3
Citric acid (mg)	3	3	3	3	3	3	3	3
Aspartame (mg)	1	1	1	1	1	1	1	1
TOTAL (mg)	250	250	250	250	250	250	250	250

Table : 2 Powder flow properties

Fomulation code	Angle of repose (θ)	Bulk density(g/cm^3)	Tapped density(g/cm^3)	Carr's index (%)	Hausners ratio
F1	31.01	0.5348	0.7438	20.09	1.39
F2	32.09	0.5850	0.7431	21.27	1.27
F3	27.04	0.6662	0.7321	9.00	1.09
F4	32.23	0.6421	0.7613	15.65	1.18
F5	34.56	0.6480	0.7213	10.16	1.11
F6	30.89	0.6613	0.7821	15.44	1.18
F7	29.64	0.6702	0.7812	14.20	1.16
F8	30.12	0.5976	0.7564	16.45	1.17

Table : 3 Physical parameters of buccal tablets of simvastatin

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Surface pH
F1	3.78	4.5	0.43	252	86.40	6.23
F2	3.72	4.3	0.41	253	85.30	6.20
F3	3.74	4.5	0.42	249	91.76	6.32
F4	3.77	4.2	0.58	248	84.50	6.30
F5	3.72	4.1	0.47	249	83.34	6.13
F6	3.76	4.0	0.37	251	87.65	5.98
F7	3.73	4.0	0.39	249	85.12	6.01
F8	3.53	4.4	0.42	253	87.43	6.50

Table : 4 : *In-vitro* drug release studies

Time in Hrs	**%CUMULATIVE DRUG RELEASE**							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	5	4.5	6.8	5	4.5	4.7	5.9	5.2
1	10.4	9.45	14.67	10.62	9.67	9.87	12.2	11.05
1.5	16.47	14.62	23	18.05	16.42	17.30	20.07	18.25
2	23.45	21.15	31.77	25.92	23.40	25.17	28.17	26.12
3	31.32	28.57	40.77	34.70	31.27	33.50	37.17	34.22
4	39.87	36.67	50.22	43.70	40.05	42.72	46.62	43.45
5	48.87	45.45	59.90	53.37	49.05	52.40	56.75	53.12
6	58.77	54.67	70.02	63.27	58.72	63.20	67.77	63.92
7	70.02	65.25	82.85	76.32	70.20	75.12	80.15	75.85
8	81.95	76.95	96.12	89.82	83.02	88.62	93.20	88.90

Table : 5 Kinetic modeling

Formulation	**Zero Order Correlation coefficient (r^2)**	**First Order Correlation coefficient (r^2)**	**Higuchi Correlation coefficient (r^2)**	**Korsemeyer Peppas Release Exponent (n)**	**Correlation coefficient (r^2)**
F1	0.997	0.934	0.972	0.979	0.996
F2	0.997	0.946	0.969	0.909	0.991
F3	0.998	0.823	0.981	0.996	0.997
F4	0.995	0.888	0.973	0.997	0.993

REFERENCES

1. Bentley's Text book of Pharmaceutics, E.A Rawlins. Eighth Edition ELBS:269-270
2. The theory and Practice of Industrial Pharmacy, Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig. Third Indian Edition, Varghese Publishing house Hind Rajasthan Building, Dadar Bombay 400014, 1987, 293-299
3. B. Agaiah Goud, Kumara Swamy. S and Praveen Kumar.V. Formulation and Evaluation of bioadhesive buccal tablets of Simvastatin. Journal of Advanced Pharmaceutical Sciences . 1 (1) 2011.
4. Hindustan Abdul Ahad *et al* . Fabrication and comparative evaluation of Glipizide- *Aloe Barbadensis miller* mucilage, Guar gum and Ispaghula Husk based sustain release matrix tablets. Int. J. Chem. Sci.: 2009, 7(2) : 1479-1490.
5. Aulton M E pharmaceutics-The science of dosage form design. 2nd ed. Churchill Livingstone, Spain; 2002.205
6. Banker G S, Rhodes C T. Modern pharmaceutics. 2nd ed. vol. 40. Marcel Dekker Inc (Newyork); 1990; 40: 287-300.
7. USP29-NF24 Page 3017 Pharmacopeial forum: 28(2) : 618
8. V. Ravikrishna, Y. Madhusudhan Rao, P. Chinnareddy K, Sujatha. Formulation and *in vitro* evaluation of Buccoadhesive tablets of Furosemide. International Journal of Drug Development and Research oct-Dec-2011 3(4) :351-361.
9. USP 26 NF 21 2667. Asian edition. The Official Compendia of Standards.
10. M.A. Saleem, Sudhir S. Pange, Shaikh Ahnaf Umair, Vishal Kumar Singh. Formulation and evaluation of mucoadhesive buccal tablets of sumatriptan Succinate Int J Novel Drug Deliv Tech 2011: 1 (2).