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Fabrication and Evaluation of Antihypertensive Buccal Mucoadhesive Tablet by UsingNatural Polymer

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ABSTRACT

Buccal route of drug delivery has significant attention to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Such routes have expanded important notice due to their pre-systemic metabolism or instability in the acidic environment associated with the oral administration. Along with the variety of buccal layer mucosae of the oral cavity has convenient and easily effective site for the delivery of therapeutic agents. The buccal site has rich blood supply, robust nature, short recovery times after stress or damage, lower enzymatic activity of saliva, facile removal of formulation. The delivery system provides better patient acceptance and compliance are some other prominent meritorious visages of buccoadhesive systems. Other advantages such as excellent convenience, low enzymatic activity, appropriateness for drugs or excipients with addition of permeation enhancer/ enzyme inhibitor or pH modifier present in the formulation used for local or systemic action. Simvastatin belongs to the statins which is lipid lowering group. The drug was act by inhibiting the 3-hydroxy3- methyl glutryl coenzyme A. Simvastatin is water insoluble crystalline powder. It undergoes extensive first pass metabolism in the liver which results in very low and variable oral bioavailability. The properties of drug like short half-life (2- 3 h), small dose size (5-80mg) and low molecular weight (418.57) makes it suitable candidate for administration by buccal route. This route of administration is expected to overcome the problem of poor oral bioavailability by at least avoiding the pre-systemic metabolism of the drug. The objective of present study is to develop and evaluate a buccal mucoadhesive tablet for delivery of simvastatin with using natural polysaccharides mucoadhesive polymers i.e. Guar guam, Xanthan gum, Carbopol 934P and HPMC K4M etc. in varying concentration by direct compression method. Pre-formulation studies used for purity of the drug by means of various parameters i.e. particle size, flow properties, density, partition coefficients, IR Spectroscopy and melting point determination etc. An analytical method calibration curve for purity identification will be developed for Simvastatin. The tablets evaluated parameters i.e. thickness, weight variation, hardness, friability and drug content, surface pH, swelling index, in vitro drug release, ex vivo residence time, mucoadhesive strength, ex vivo permeation etc.

Keywords: Bucco adhesive, Bioavailability, Metabolism, Drugs, Oral cavity

INTRODUCTION

Buccal Delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. A suitable buccal drug delivery system should be flexible and possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a controlled and predictable manner to elicit the required therapeutic response [1]. Mucoadhesive polymers are synthetic or natural macromolecules which are capable of attaching to mucosal surfaces. Consequently, other absorptive mucosas are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery [2]. The oral cavity can be divided into two regions; the outer oral vestibule which is bounded by lips and cheeks and the oral

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cavity itself. The borders being formed by the hard and soft palates, the floor of the mouth and the pillars of the fauces and tonsils. The buccal epithelium lack tight junctions common to intestinal and nasal mucosae and is endowed with gap junctions, desmosomes and hemidesmosomes, which are loose intercellular links [3]. For mucosal and transmucosal administration, conventional dosage forms are not able to assure therapeutic drug levels in the mucosa and circulation because of the physiological removal of the oral cavity (washing effect of saliva and mechanical stress), which take the formulation away from the mucosa, resulting in a very short exposure time and unpredictable distribution of the drug on the site of action/absorption. The therapeutic requirements, formulations for buccal administration should contain: mucoadhesive agents, to maintain an intimate and prolonged contact of the formulation with the absorption site; penetration enhancers, to improve drug permeation across mucosa (transmucosal delivery) or into deepest layers of the epithelium (mucosal delivery), enzyme inhibitors, to protect the drug from the degradation by means of mucosal enzymes and solubility modifiers to enhance solubility of poorly soluble drugs [4,5]. Bioadhesive drug delivery systems can be achieved by coupling bioadhesion characteristics to microspheres and developing novel delivery systems referred to as "bioadhesive microspheres" [6]. Bioadhesion in simple terms can be described as the attachment of a synthetic or biological macromolecule to a biological tissue. The mechanism of bioadhesion has been reviewed extensively. Adhesion between mucin and mucoadhesive polymers is usually analyzed based on the molecular attractive and repulsive forces [7]. Simvastatin is a lipid-lowering agent that is derived synthetically from the fermentation of Aspergillus terreus. It is a potent competitive inhibitor of 3- hydroxy-3-methylglutaryl coenzyme. A reductase (hydroxymethylglutaryl COA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It may also interfere with steroid hormone production. Due to the induction of hepatic LDL receptors, it increases breakdown of LDL cholesterol and for the treatment of hypercholesterolemia and for the reduction in the risk of cardiac heart disease mortality and cardiovascular events. It can also be used in adolescent patients for the treatment of heterozygous familial hypercholesterolemia. Simvastatin, the methylated form of lovastatin, is an oral antilipemic agent which inhibits HMG-CoA reductase. Simvastatin is used in the treatment of primary hypercholesterolemia and is effective in reducing total and LDL-cholesterol as well as plasma triglycerides and apolipoprotein B. Simvastatin is a prodrug in which the 6-membered lactone ring of simvastatin is hydrolyzed *in vivo* to generate the beta, delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). Once hydrolyzed, simvastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. Interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholesterol. The objective of present study is to develop and evaluate a buccal mucoadhesive tablet for delivery of simvastatin with using natural polysaccharides mucoadhesive polymers i.e. Guar guam, Xanthan gum, Carbopol 934P and HPMC K4M etc. in varying concentration by direct compression method. The tablets evaluated paramaters i.e. thickness, weight variation, hardness, friability and drug content, surface pH, swelling index, *in vitro* drug release, *ex vivo* residence time, mucoadhesive strength, *ex vivo* permeation etc.

MATERIAL AND METHODS

Preformulation study is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable & bioavailable dosage forms which can be mass produced. Obviously, the type of information needed depend on the dosage form to be developed. Even after developing a formulation and method of manufacture on these principles, it is still necessary to confirm stability and bioavailability, but there is a smaller probability that the formulation will fail. If two or three formulations are developed in parallel, there is even greater probability that one will be significantly minimize the risks of failure and increase the likelihood of producing a high quality. The study contains physical evaluation, solubility, melting point, determination of pH, loss on drying, flow properties, bulk properties, tapped density, compressibility index, hausner ratio and determination of λ_{max} of drug simvastatin etc.

Preparation of simvastatin buccal tablet

Direct compression was taken after to manufacture the buccal tablets of Simvastatin. Six different formulations (SF1 - SF6) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in **Table 1** and all the definition were utilized for encourage assessments parameters. Excipients like Sodium bicarbonate, citrus extract anhydrous, Magnesium Stearate were selected for the examination. Carbopol as buccal mucoadhesive polymers. Steps associated with the manufacture of tablets, first the medication; polymer and different excipients selected were gone through 40 mesh sieves. Required amount of medication, polymer and excipients were weighed legitimately and moved into polyethylene pack and the mix was blended for no less than 15 min. The mix acquired was then lubricated by including 1% magnesium stearate and again blended for another 5min.

Table 1. Various formulations of Simvastatin buccal tablets [8].

Excipients (mg)	SF1	SF2	SF3	SF4	SF5	SF6
Simvastatin	10	10	10	10	10	10
HPMC K 4	40	50	40	50	-	-
Carbopol	-	-	40	50	40	50
Na Alginate	-	-	-	-	40	50
Magnesium stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Lactose	80	70	40	20	40	20
Total Weight	150	150	150	150	150	150

Characterization of tablets: All the tablets were evaluated for following various parameters which includes following parameters

General Appearance: Withdrawn 10 tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter: Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Uniformity of weight: Twenty tablets were randomly selected from each batchindividually weighed, the average weight and standard deviation of 20 tablets was calculated.

Hardness: For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach).

Friability: The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 min. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Drug content: Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of phosphate buffer pH 6.8 and made up to volume with of phosphate buffer pH 6.8. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 248nm using of phosphate buffer pH 6.8 as blank.

Swelling Index: Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and phosphate buffer pH 6.8 was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 h (W_2). Percent hydration (swelling index) was calculated using the following formula: Swelling index = $(W_2 - W_1) \times 100/W_2$

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet

***In-vitro* dissolution rate studies:** *In vitro* drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml phosphate buffer pH 6.8 was set into the dissolution flask maintaining the temperature of 37±0.5°C and rpm of 75. One simvastatin tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 h. Sample measuring 5 ml were pulled back after each 1 h up to 2 h using 10ml pipette. The new disintegration medium (37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 248.0 nm using spectroscopy. The quantitative analysis of the qualities got in dissolution/release tests is simpler when mathematical formulas that express the dissolution comes about as an element of a portion of the measurement frames attributes are utilized. The pharmaceutical dosage frames following this profile release a similar measure of medication by unit of time and it is the ideal method of medication release keeping in mind the end goal to accomplish a pharmacological prolonged action [8].

RESULT AND DISCUSSION

The sensory characters of prepared simvastatin drug were white to off-white powder, Odorless and tasteless characteristics. The solubility of Simvastatin drug in distilled water is sparingly soluble, 0.1 N Hydrochloric acid is slightly soluble, ethanol and methanol are freely soluble, and phosphate buffer pH 6.8 is soluble. The Melting point of Simvastatin is 136-138°C and average pH of solution of drug is 7.37.

The average percent of loss of drying is 1.1%. The flow properties of drug were estimated in terms of Carr's index, Hausners ration and angle of repose and it was 6.722 % CI, 1.072 HR and 23.12° Angle of repose. The linear regression analysis was done on Absorbance data points. The results are as follow for standard curve was determined and it was Slope 0.009, intercept 0.012 and correlation coefficient (r^2) is 0.997. The prepared formulations were optimized with various parameters and pre-compression properties of simvastatin mucoadhesive granules were good flow in nature (**Tables 2 & 3**). The optimization of post compression properties of simvastatin buccal mucoadhesive tablets (n=3). The Thickness (mm) varied from 2.83 - 2.89 mm, Hardness were varied from 4.2 - 4.5 kg/cm^2, Weight variation were varied from 149 - 155 mg, Friability were varied from 0.745 -0956 % and drug content were varied from 98.89 - 99.56 % (**Table 4**). The swelling index of simvastatin buccal tablets after 12 h was varied from 73.25 - 80.21 % (**Table 5**). The invitro drug release study was carried out and when the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 0.965 hence indicating drug release from formulations was found to follow first order kinetic **(Figures 1-9)**.

Table 2. Calibration curve of Simvastatin in phosphate buffer pH 6.8 [9].

S. No.	Conc. (µg/ml)	Absorbance
1	0	0
2	10	0.117
3	20	0.213
4	30	0.318
5	40	0.398
6	50	0.497

Table 3. Optimization of pre-compression properties of Simvastatin.

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner's ratio
SF1	0.485	0.585	17.094	1.206
SF2	0.478	0.586	18.430	1.226
SF3	0.486	0.579	16.062	1.191
SF4	0.485	0.586	17.235	1.208
SF5	0.473	0.581	18.589	1.228
SF6	0.476	0.579	17.789	1.216

Table 4. Optimization of post compression properties of Simvastatin buccal tablets (n=3).

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
SF1	2.89	4.2	155	0.856	99.12
SF2	2.85	4.3	152	0.785	99.25
SF3	2.83	4.4	149	0.882	99.56
SF4	2.84	4.5	153	0.745	98.89
SF5	2.83	4.3	154	0.956	99.12
SF6	2.83	4.2	150	0.855	98.96

Table 5. Optimization of Swelling Index of Simvastatin buccal tablets [9].

Formulation Code	% Swelling Index			
	2 h	4 h	8 h	12 h
SF1	22.36	43.56	63.25	73.25
SF2	24.36	44.58	68.89	75.65
SF3	23.45	43.36	65.52	74.58
SF4	28.89	54.57	69.98	79.85
SF5	29.45	55.45	70.23	80.21
SF6	26.45	56.74	72.45	78.25

Table 6. *In-vitro* drug release study of buccal tablets.

Time (h)	% Cumulative Drug Release					
	SF1	SF2	SF3	SF4	SF5	SF6
0.5	33.25	32.25	30.14	25.56	20.36	18.56
1	45.56	40.23	39.98	32.25	26.65	22.25
1.5	65.56	60.58	59.88	46.69	40.23	39.98
2	88.89	79.98	78.89	58.89	51.12	49.98
3	98.89	87.52	85.56	69.98	60.23	55.56
4	-	93.32	92.23	76.12	71.45	69.78
6	-	98.85	99.12	88.56	79.98	78.89
8	-	-	-	92.23	86.65	83.32
12	-	-	-	98.78	90.12	89.98

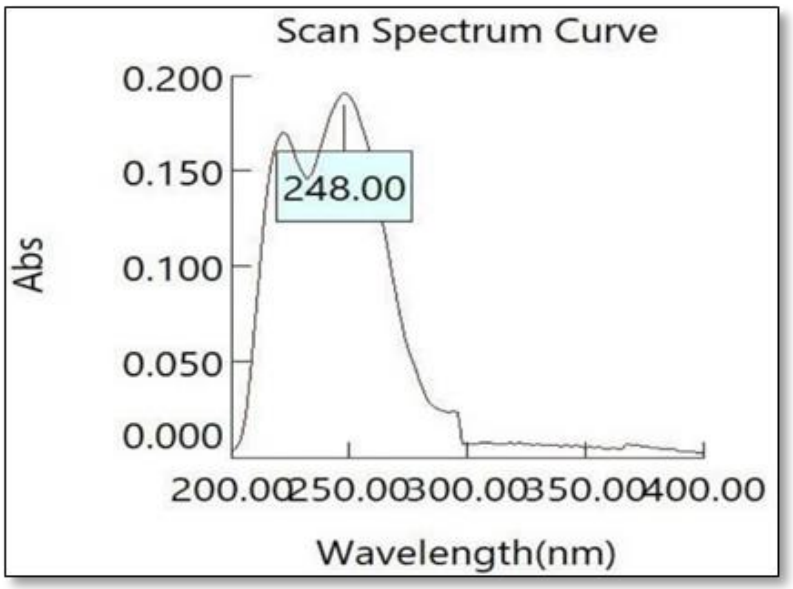

Figure 1. Wavelength maxima of Simvastatin in phosphate buffer pH 6.8 at 248nm [9].

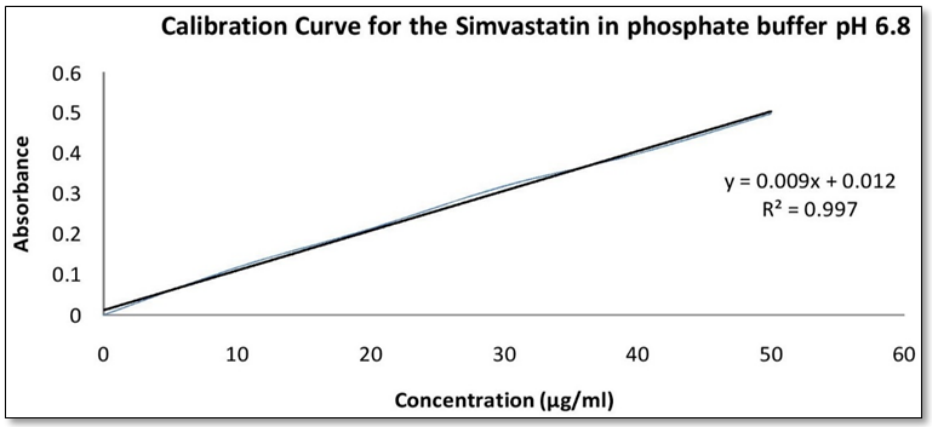

Figure 2. Calibration curve of Simvastatin in phosphate buffer pH 6.8 at 248nm [9].

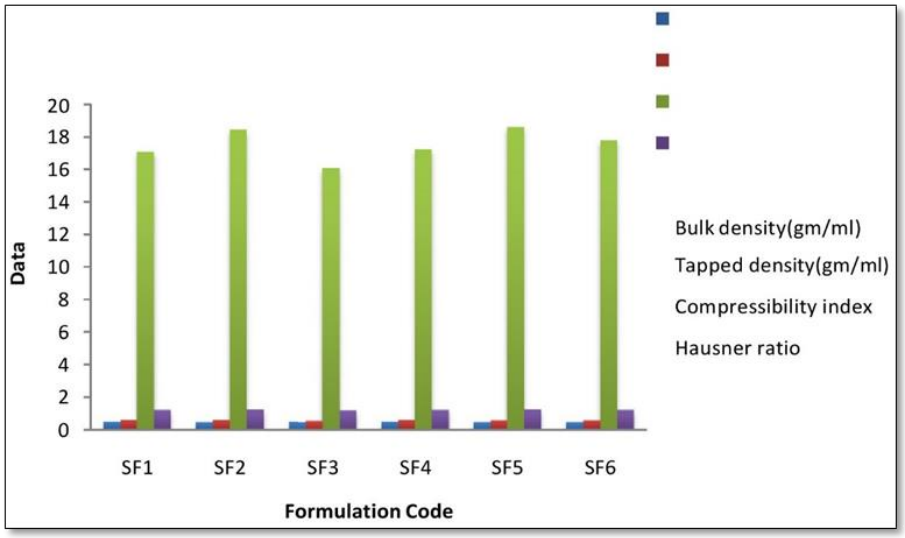

Figure 3. Optimization of pre-compression properties of Simvastatin [10].

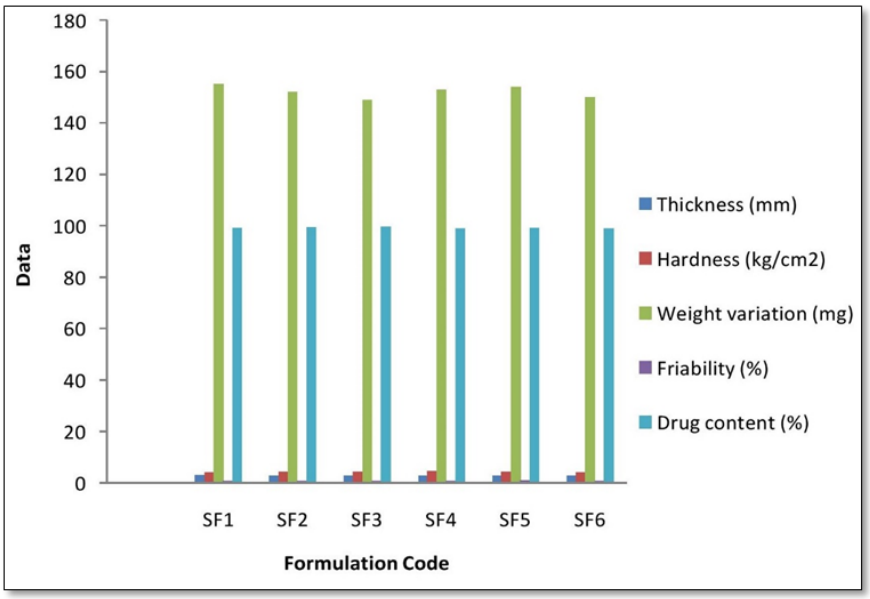

Figure 4. Optimization of post compression properties of Simvastatin buccal tablets [10].

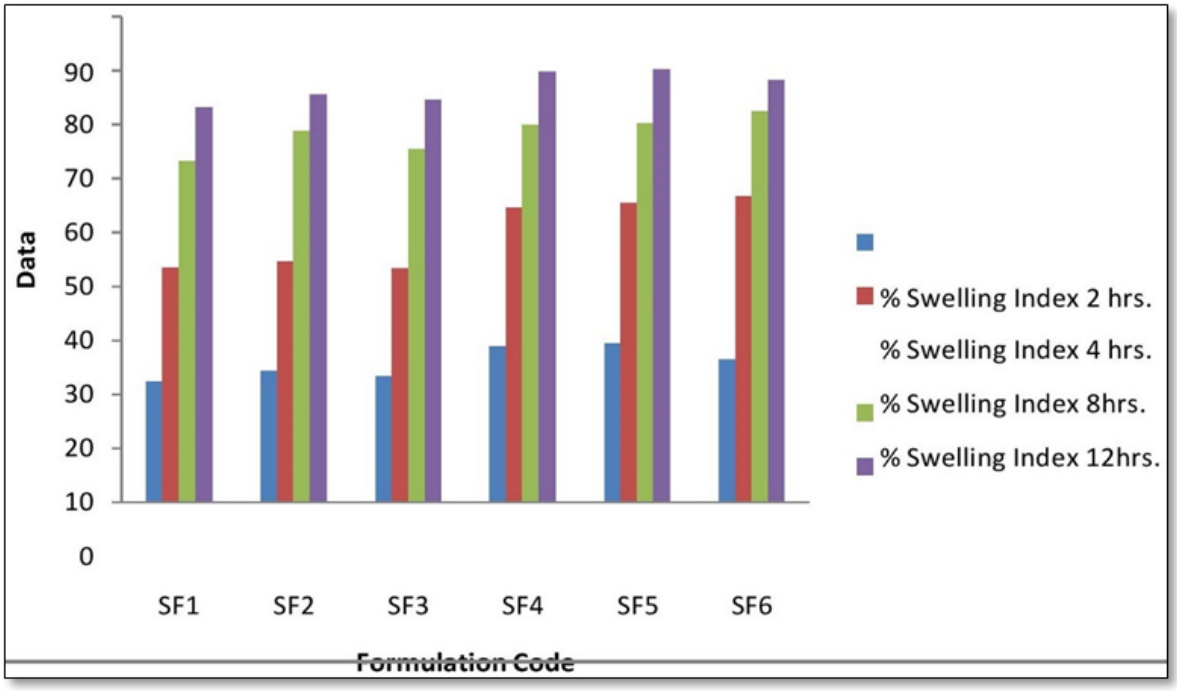

Figure 5. Optimization of Swelling Index of Simvastatin buccal tablets [10].

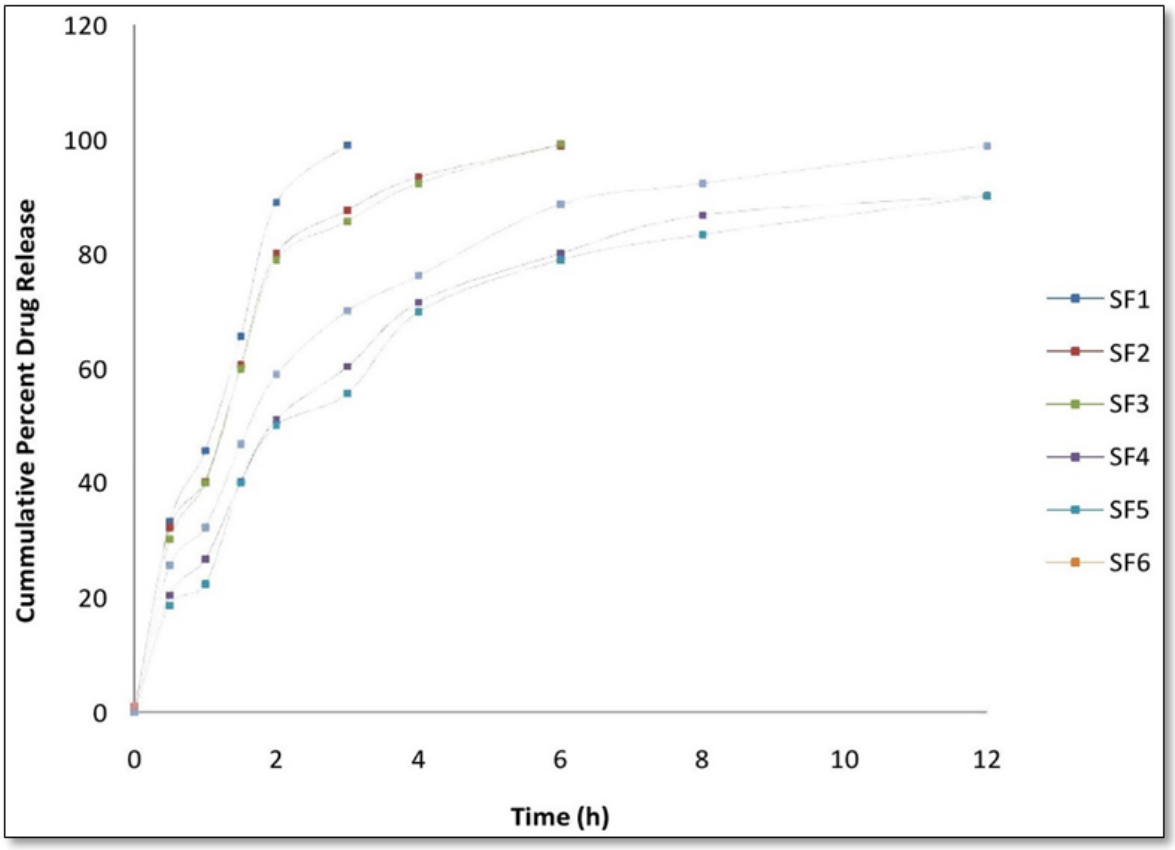

Figure 6. Zero-order kinetics *in vitro* drug release study of buccal tablets [11].

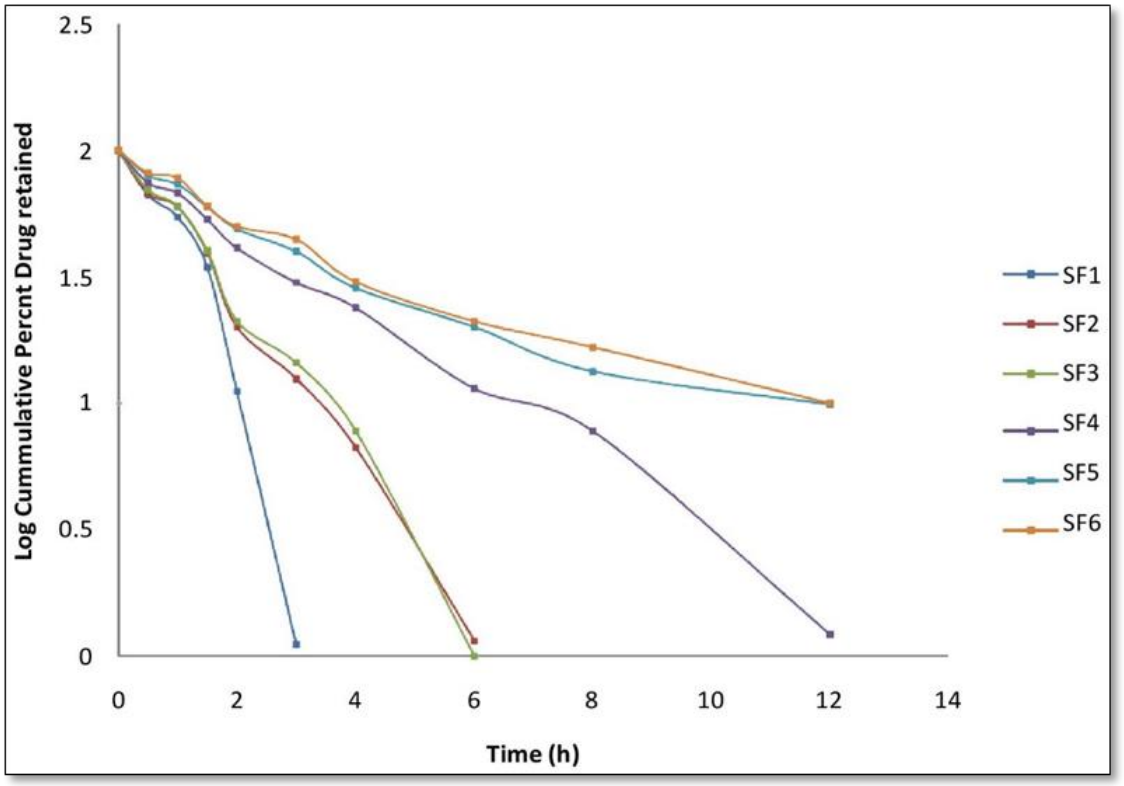

Figure 7. First-order kinetics *in vitro* drug release study of buccal tablets [11].

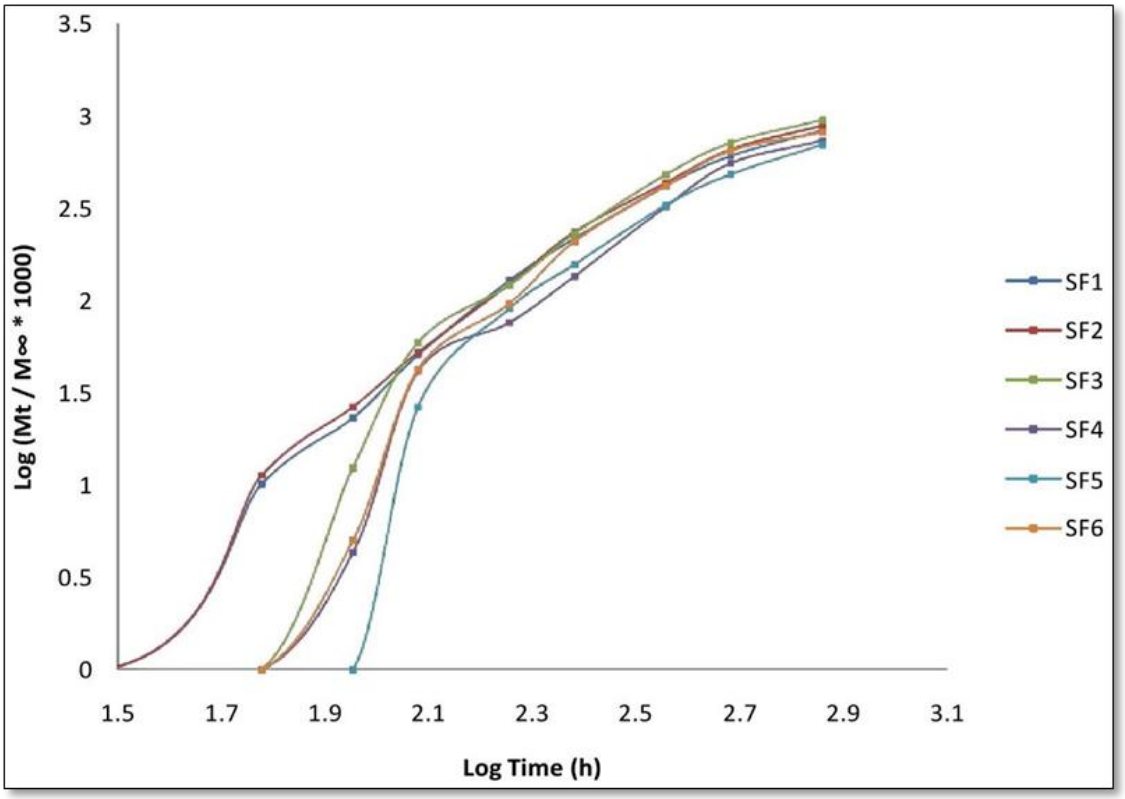

Figure 8. Korsmeyer-peppas kinetics *in vitro* drug release study of buccal tablets [11].

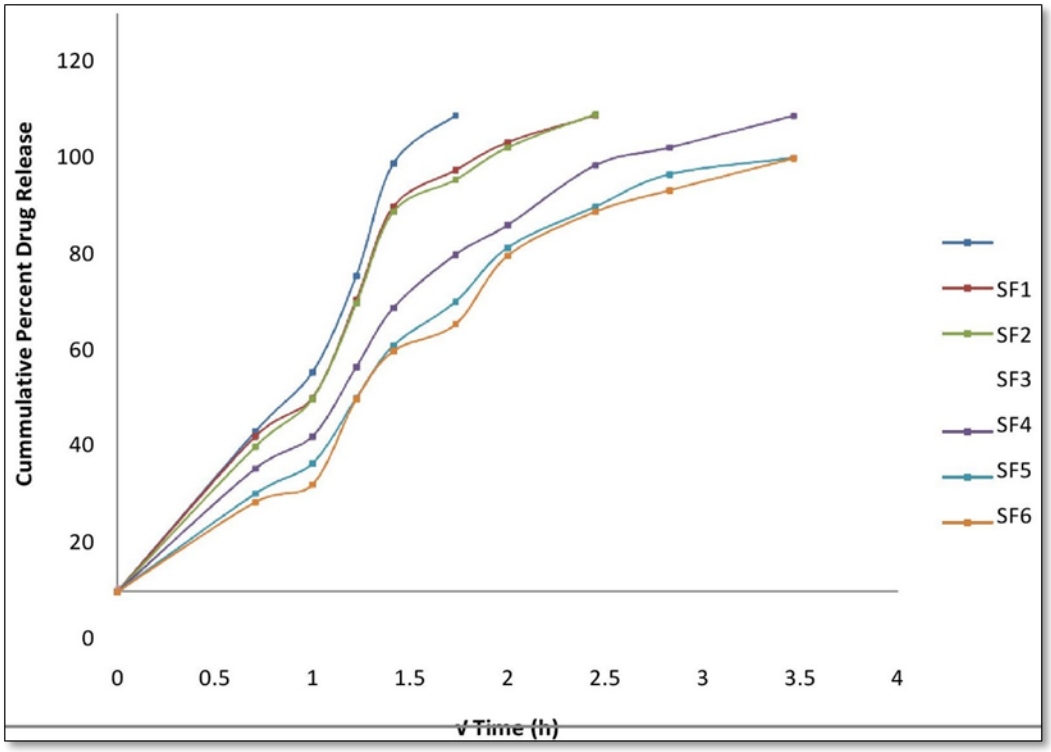

Figure 9. Higuchi kinetics *in vitro* drug release study of buccal tablets [12].

SUMMARY AND CONCLUSION

From the present study the following conclusions were made. Buccal tablets of Simvastatin using HPMC K4, Carbopol 934 and Na Alginate prepared by direct compression method were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations of tablets prepared. Low values of standard deviations indicate uniform distribution of drugs within the matrices. The drug polymer ration influenced the release of drug from the formulations. An increase in polymer decreased the drug release. Formulation SF4 with drug polymer (HPMC K4, carbopol and Na Alginate) has shown promising results as per USP test II requirements. Among these formulations SF4 is acceptable for further pharmacodynamic and pharmacokinetic evaluation.

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