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Formulation and Evaluation of Buccal Patches of Simvastatin by Using Different Polymers

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The objective of this study was to develop mucoadhesive buccal 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. From the present study carried out on simvastatin buccal patches prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC. The buccal patches prepared using 50% glycerine w/w of polymer weight were found to have good physical characteristics. The mean thickness of buccal polymeric patches increased with an increase in the amount of polymer percent. Eudragit RS-100 HPMC (1:2) containing 50% glycerine w/w of polymer weight had is maximum thickness. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with time and with an increase in hydrophilic polymer. Eudragit-RS100-HPMC buccal patches better swelling index, , folding endurance followed by Eudragit-RS100-HPMC, Eudragit-RS100-PVA and Eudragit-RS100-PVP buccal patches. . The increase in the amount of polymer retarded the release of simvastatin. F1 (eudragit-RS100-PVP) showed the maximum and faster release. Simvastatin was incorporated in the selected polymeric patches and these were then evaluated for content uniformity and in vitro release. Higher drug release was obtained.

Keyword: Buccal Mucosa, Transmucosal Drug Delivery, Buccal Patches, Simvastatin, Polymers, Bio Adhesion, In Vitro release.

INTRODUCTION: Historically, the oral route of drug administration has been the one used most for both conventional as well as novel drug delivery.

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The reasons for this preference are obvious because of the ease of administration and widespread acceptance by patients**.** Major limitations of oral route of drug administration are Some drugs irritate the gastrointestinal tract and this is partially counteracted by coating. Oral route may not be suitable for drugs targeted to specific organs.The conventional type of buccal dosage forms are buccal tablets, troches and lozenges, and mouth washers. Amongst the

various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity)[1]. Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.[3]

Simvastatin is a Hypolipidemic used to control elevated cholesterol, or hypercholesterolemia. It is a member of the Statin class of pharmaceuticals. Simvastatin is a synthetic derivate of a fermentation product of *Aspergillus terreus*. The drug is marketed under the trade name Zocor, as well as generically. The primary uses of simvastatin is for the treatment of dyslipidemia and the prevention of cardiovascular disease. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels. All statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway responsible for the endogenous production of cholesterol. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration. The $t_{1/2}$ for simvastatin is 2 to 4 hrs and bioavailablity is 5% and efficiency of protein binding is 95%.[4,5]

MATERIALS AND METHOD :-

Materials:-

Simvastatin was a gift sample from Ind swift pharmaceutical pvt. lmtd.Chandigarh (India) Hydroxy propyl methyl cellulose,Ethyl cellulose and Eudragit RS 100 were obtained from Central drug house pvt. Ltd. And other chemicals used were of analytical grade and produced from central drug house (New Delhi,India) Concentrations of simvastatin were measured with a uv-vis spectrometer And polymers was verified using FTIR,and UV-VIS spectrometric methods

Methods

Preparation of polymeric solution:-

Accurately weighed quantity of PVP was dispersed in 5% ethanol aqueous solution. Required amount of eudragit RS 100 was then dissolved in the solution. This polymeric solution was then kept for 24 hours in a sonicator and then it was filtered through a muslin cloth. Glycerine (plasticizer) was then added to the polymeric solution in the desired ratio 10 ml of the resultant

mixture was poured into each fabricated glass ring placed on a mercury substrate. Drying was carried out at 45ºC for 24 hours in hot air oven, resultant polymeric patches had a diameter of 6.2 cm. The patches obtained were used as such or cut into a diameter of 1 cm² for different evaluation studies. Similar procedure was carried out for the preparation of eudragit-PVA, eudragit-HPMC, eudragit-EC polymeric patches. The glycerine was used as plasticizer in percent of 20%, 30% and 50% w/w of polymer weight.**:-**

Method of Preparation:

Calculated amount of simvastatin (30 mg/cm²) was dispersed in the polymeric solution, after the drug is completely dispersed, glycerine (plasticizer) was added and stirred to form a uniform dispersion. The dispersion was casted onto the mercury substrates kept in the hot air-oven at 45ºC for 24 hours. The patches thus formed were removed and stored between butter paper in a dessicator.

EVALUATION OF BUCCAL PATCHES:

Thickness uniformity of the patches[6]:-

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.

Folding endurance[7]:-

Folding endurance of the patches was determined (Khanna *et al.,* 1997) by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on five patches.

Drug content uniformity of the patches[8]:-

The patches were tested for the content uniformity. A patch of size 1×1 cm2 was cut and placed in a beaker. Ten ml of a 0.1 N hydrochloric acid solution was added. The contents were stirred in a cyclo-mixer to dissolve the film. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 248 nm.

Swelling studies of the patches[9]]

Weight and area increase due to swelling were measured (Gua and Cooklock, 1995). Weight increase due to swelling: A drug-loaded patch of 1x1 cm2 was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every five min, the cover slip was removed and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.Area increase due to swelling: A drug loaded patch size of 1x1 cm2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, %S, was calculated using the following equation:

$$\%S = \frac{X_t - X_o}{X_o} \times 100$$

where Xt is the weight or area of the swollen patch after time t and Xo is the original patch weight or area at zero time.

Tensile strength of the patches[10]:-

Tensile strength of the patch was determined with Digital Tensile Tester (DY-20, Adamulthomargy, France 1986).

Table No:1 : Composition of different buccal mucoadhesive formulations containing Simvastatin

Ingridient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Simvastatin(mg)	20	20	20	20	20	20	20	20	20	20	20	20
Eddragit RS-100	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
PVP	1%	1.5%	2%	-	-	-	-	-	-	-	-	-
PVA	-	-	-	1%	1.5%	2%	-	-	-	-	-	-
HPMC	-	-	-	-	-	-	1%	1.5%	2%	-	-	-
EC	-	-	-	-	-	-	-	-	-	1%	1.5%	2%
Ethanol	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Glycerine(percent w/w of polymeric weight)	50	50	50	50	50	50	50	50	50	50	50	50

Table 2: Characteristics of buccal mucoadhesive patches containing Simvastatin

Formulation code	Thickness (mm)	Folding endurance	Content uniformity (mg)	Percentage swelling index in time (min)				Tensile strength
				5	10	30	60	
F1	0.2048	96.55	0.5217	3.57	9.49	22.06	27.46	1.4168
F2	0.220	96.00	0.5225	3.68	9.87	23.37	27.97	1.7068
F3	0.227	104.80	0.5209	5.45	9.89	23.47	28.49	1.8568
F4	0.256	105.35	0.5231	5.94	12.63	23.80	31.18	1.9368
F5	0.291	106.88	0.5224	6.10	13.55	24.65	34.70	2.047
F6	0.2968	109.88	0.5254	6.77	13.96	27.67	34.78	2.118
F7	0.3295	115.00	0.5223	7.16	17.64	33.46	42.0	1.889
F8	0.34488	125.00	0.5215	8.49	18.85	33.89	44.54	1.9635
F9	0.3565	132.88	0.5242	8.80	19.30	37.89	53.68	2.128
F10	0.3585	155.35	0.5242	10.12	19.60	39.70	45.69	2.1935
F11	0.3686	162.55	0.5231	12.83	22.80	44.80	50.68	2.26
F12	0.390	16 7.00	0.5250	15.88	24.98	44.89	54.74	2.495

The sensitivity range of the machine is 1 to 10 Newtons. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (5×3 cm2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the patch was taken directly from the dial reading in Newtons, which was converted into kilograms.

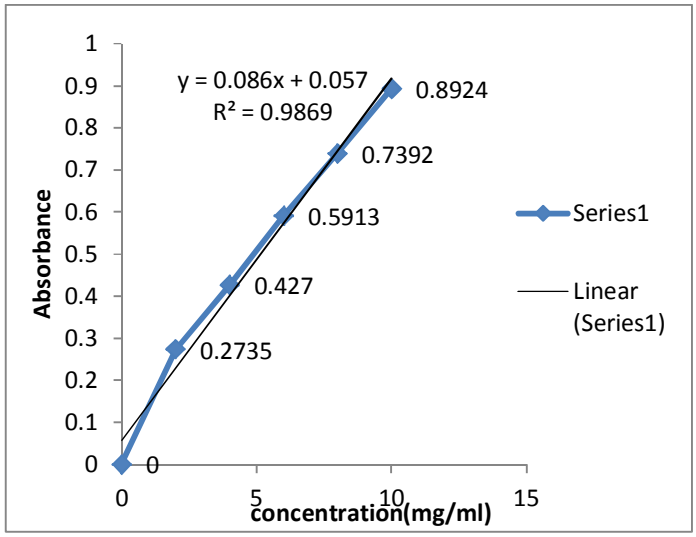
In vitro release studies of simvastatin patches in phosphate buffer (pH 7.2)[11]:-

A patch of 1x1 cm2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 7.2). This slide was kept at an angle of 45° in a 250 ml beaker containing 100 ml of phosphate buffer (pH 7.2) solution. The beaker was kept in circulating water bath in which the temperature was maintained at 37°C. A non-agitated system was selected to eliminate any effect of turbulence on the release rate (Borodkin and Tucker, 1974). Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). The slide was quickly reintroduced into the beaker. Five ml of the buffer was replaced immediately and the beaker was kept covered with a petridish to prevent evaporation of the fluid. The samples were taken after every 10 min upto 90 min. and analyzed for drug content at 238 nm. The release studies were conducted for three times and average was determined.

RESULTS AND DISCUSSION

Calibration curve of simvastatin in 0.1 N HCl and phosphate buffer (pH 7.2) solutions were obtained at λmax 238 nm with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 2-10 µg/ml. Analyses were done in triplicate which shown in fig 1.

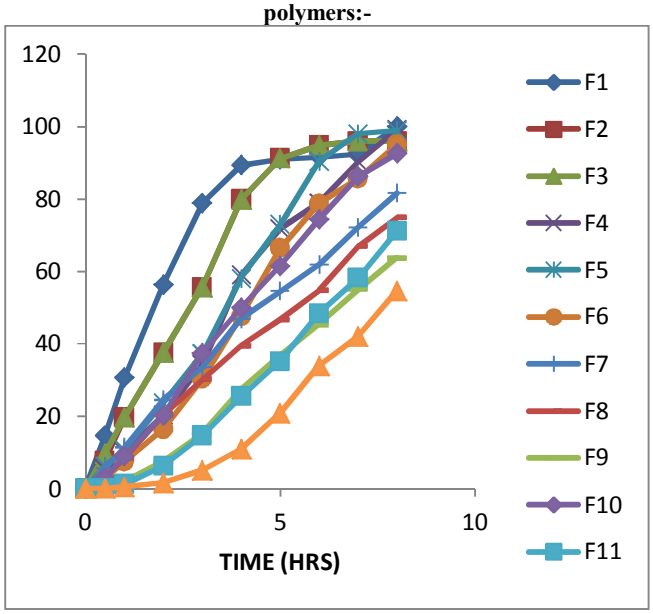
Figure no:1 Calibration curve of Simvastatin



From the present study carried out on simvastatin buccal patches prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC the following points can be concluded. The buccal patches prepared using 50% glycerin w/w of polymer weight were found to have good physical characteristics. The mean thickness of buccal polymeric patches increased with an increase in the amount of polymer percent. Eudragit RS-100 HPMC (1:2) containing 50% glycerine w/w of polymer weight had is maximum thickness. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with time and with an increase in hydrophilic polymer. Eudragit-RS100-HPMC buccal patches better swelling index, folding endurance followed by Eudragit-RS100-HPMC, Eudragit-RS100-PVA and Eudragit-RS100-PVP buccal patches.

Simvastatin was incorporated in the selected polymeric patches and these were then evaluated for content uniformity and *in vitro* release.in fig 2. Higher drug release was obtained from eudragit-RS100-PVP patches followed by eudragit-RS100 -PVA, eudragit-RS100 -HPMC and - eudragit-RS100- EC F1 (chitosan-PVP 1:1) showed the maximum and fastest release t50% 1.7 hours, D8 hrs 99.95%. In vitro release characteristics of Simvastatin buccal patches showed

Figure no-2 Percentage cumulative drug release of various formulations of simvastatin by using different polymers:-



decrease in percent release with an increase in the amount of polymer, required for 50% of release was found to be maximum for F12 (7.6 hours) followed by F9 (6.5 hours) and F11 (6.2 hours), the least t50% 1.7 hours was observed for F1 simvastatin buccal patches The maximum release of 99.95% was observed for F1 (eudragit-RS100-PVP) followed by F5 (eudragit-RS100-PVA), eudragit-RS100-HPMC and eudragit-RS100-EC showed relatively retarded release with the least release observed for F12 54.6% in 8 hours.

Conclusion:- From the present study carried out on simvastatin buccal patches prepared from 1% Eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC the following points can be concluded. The buccal patches prepared using 50% propylene glycol w/w of polymer weight were found to have good physical characteristics. The mean thickness of buccal polymeric patches increased with an increase in the amount of polymer percent. Eudragit-RS100-EC (1:2) containing 50% glyecrine w/w of polymer weight had is maximum thickness. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with time and with an increase in hydrophilic polymer. Thus, one may conclude that these polymer systems of eudragit-RS100 along with PVP, PVA, HPMC and EC have potential for consideration for drug delivery as buccal dosage forms.

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