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FORMULATION AND EVALUATION OF SUSTAINED RELEASE BUCCAL TABLETS OF SIMVASTATIN FOR UNIDIRECTIONAL RELEASE

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ABSTRACT

The present work is based on "Formulation and Evaluation of Sustained Release Buccal Tablets of Simvastatin for Unidirectional Release". Simvastatin has short biological half-life (3hr), high first-pass metabolism and poor oral bioavailability (5%), hence an ideal candidate for buccal delivery system. For poorly water-soluble drugs that do not show pH dependent solubility, an approach to increase the dissolution rate is the addition of surfactants to the dissolution media. Ethyl cellulose was used as backing layer to prepare buccal bilayered tablet for unidirectional release by Wet Granulation method. Formulations were evaluated for mass variation, hardness, friability, drug content, swelling studies, in-vitro release studies in pH 6.8 phosphate buffer and in-vitro bio adhesion studies through porcine buccal mucosa. In vitro release profiles of all the batches were performed with the kinetic model studies. Formulation F06 selected as optimized formulation based on physicochemical parameters and follows Zero order release. FTIR studies show no evidence on interaction between drug, polymers and other excipients. The final optimized batch was kept for 3 months of stability study according to ICH guidelines and formulation was found to be stable after 3 months of study. The optimized batch was studied for the dissolution kinetic modelling.

KEYWORDS

Ethyl cellulose, Unidirectional release, Simvastatin, Swelling index and Buccal drug delivery.

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INTRODUCTION[1]

The conventional dosage form releases drug rapidly and creates the absorption pool at the site of absorption and thus attains a high plasma drug concentration. Hence, the rate of absorption becomes the rate-limiting step. But in case of sustained release or controlled release dosage forms the drug is released for prolonged period along the entire length of the GIT. Here the rate of release of

drug from the dosage form becomes less when compared to rate of absorption. Hence the rate of release of drug becomes the rate-limiting step. The term "sustained release" is used to describe the pharmaceutical dosage form formulated to retard the release of drug such that its appearance in systemic circulation is delayed or prolonged & its plasma profile is sustained.

The goal of using sustained release formulations is to maintain an effective therapeutic concentration of the drug for an extended period of time. Especially drugs with a short half-life are good candidates for this formulation. The rate of drug release equals the rate of drug elimination, thus ensuring that the drug concentration is within the therapeutic window for about 24 hours. With these formulations, the initially high release rate seen with a traditional formulation is decreased and the decline period is slowed down. However, the limiting step is the drug diffusion out of the formulation that is influenced by the matrix pores, additives and the wettability of the formulation.

Sustained release dosage forms can be divided into monolithic formulations and multiple-unit dosage forms. There are a lot of interests in the multiple-unit dosage forms, thanks to their pharmacokinetic properties and flexibility: these particles are

very small and are spread more uniformly in the intestinal tract; the gastric emptying and the feeding state don't have an influence on the spreading; and high local concentrations and dose dumping seen with monolithic dosage forms are avoided. Different types of drug release mechanisms are shown in the Figure No.1.

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 administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore mucoadhesive dosage forms were suggested for oral drug delivery which includes adhesive tablets, adhesive gels and adhesive patches.

Simvastatin is a prodrug and is hydrolyzed to its active β-hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

The aim of current study was design, formulation and evaluation of SUSTAINED RELEASE BUCCAL TABLETS OF SIMVASTATIN using hydroxy propyl methyl cellulose k4m and Sodium Carboxy Methyl Cellulose as polymers and evaluated by suitable methods for optimized formulation.

MATERIAL AND METHODS[2]

Materials and Chemical

Hydroxy propyl methyl cellulose k4m, Sodium Carboxy Methyl Cellulose, Mannitol, Micro crystalline cellulose, Sodium lauryl sulphate, Ethyl cellulose, BHT and Magnesium stearate. All chemicals are provided by Narasaraopet institute of Pharmaceutical Sciences. The formula for all formulations is showed in the Table No.1.

Method

The granules were prepared by wet granulation method and warm water was used as granulating agent for drug layer. Accurately weighed quantities of the ingredients were mixed in a glass mortar and required quantity of granulating agent was added to the powdered mass and mixed thoroughly. The granules were prepared by passing the wet mass through British Standard Sieve (BSS) No.16. Wet granules were dried in hot air oven for 30 min at 60^{o}C and then passed through BSS No.22.

Finally, required quantity of the drug containing granules were placed on the pre compressed backing layer and recompressed into tablets of 8 mm diameters as to provide unidirectional release by

double compression method. In each batch, 20 tablets were compressed.

EVALUATION PARAMETERS[1,2]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

The FT-IR results of pure drug and drug with polymers showed in fig. No.4,5 and 6.

Pre-compression studies of tablet granules

Bulk density

3gm of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

$$\theta = Tan^{-1} (h/r)$$

Where,

θ = Angle of repose,

h = Height of the powder cone,

r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density**,** BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

All the flow properties results are measured and tabulated in table no.2.

Formula

Hausner's Ratio = Tapped density/Bulk density

Evaluation of tablets[3, 4, 5]

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Sustained release tablets have a hardness of 10 -20 kg ; however, Oral disintegrating tablets normally have a hardness of 4 to 10 kg and hypodermic and chewable tablets have a hardness of 3 kg.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calipers and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and

reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight **F** - Final weight

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong- Cobb hardness test. Friability of the tablets was determined in a Roche friabilator. The thickness of the tablets was measured by Vernier caliper. Weight variation test was performed according to the official method.

All the tablets evaluation tests are done and the results are tabulated in table no.3

Dissolution test[3, 4]

In vitro drug release study of bucco adhesive tablets were performed in dissolution was assessed using standard USP dissolution apparatus type II. The bowls of the dissolution apparatus was filled with 900ml of phosphate buffer pH 6.8 and maintained at a temperature of 37 0.5oc. The protocol of the dissolution apparatus was settled for automatic 1ml sample withdrawal and replacement of fresh media at predetermined time interval the dissolution apparatus was covered with the black colour polythene cover to protect the solution from light. The collected samples were filtered through the 0.45µm 81Millipore filter. The samples were analyzed for drug content using double beam UV spectrophotometer at 247nm.

RESULTS AND DISCUSSION

The tablets were evaluated for different parameters like weight variation, thickness, hardness, drug content and invitro evaluation studies and stability studies. Observations of all the formulations form physical characterization have shown that the formulations show optimum results.

Drug content results are showed in the table no.4. The Invitro drug release of different formulations are tabulated in table no.5. Standard curve for simvastatin values are showed in the table no.6.

Table No.1: Formula

Components	F1	F2	F3	F4	F5	F6	F7	F8	F9
Simvastatin	40	40	40	40	40	40	40	40	40
HPMC K4M	20	20	20	35	35	35	50	50	50
SCMC	20	40	60	20	40	60	20	40	60
MCC	25	25	25	25	25	25	25	25	25
SLS	5	5	5	5	5	5	5	5	5
Mannitol	78	58	38	63	43	23	48	28	8
BHT	4	4	4	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Hydro Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Backing layer Ethyl cellulose	76	76	76	76	76	76	76	76	76

Table No.2: Flow Properties

Formulation code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (degrees)
F1	0.44 0.00	0.55 0.00	20.33 0.57	1.25 0.00	14.51 0.84
F2	0.32 0.00	0.37 0.00	12.62 0.56	1.14 0.01	21.43 0.00
F3	0.36 0.00	0.56 0.00	13.62 0.63	1.18 0.03	23.73 0.41
F4	0.39 0.00	0.47 0.01	17.29 2.10	1.20 0.01	22.33 3.27
F5	0.44 0.00	0.54 0.00	18.32 0.57	1.22 0.02	26.81 5.85
F6	0.19 0.00	0.26 0.00	29.31 1.16	1.40 0.02	28.64 4.07
F7	0.29±0.00	0.38±0.00	24.66±0.58	1.32±0.01	34.66±5.58
F8	0.31±0.00	0.38±0.01	18.65±2.32	1.23±0.03	30.09±5.08
F9	0.18±0.00	0.27±0.00	33.98±0.00	1.51±0.00	29.69±2.06
Backing layer EC	0.22±0.00	0.33±0.00	32.99±0.99	1.49±0.02	30.31±3.16

Table No.3: Post compression studies

Formulations	Weight Variation (%)	Thickness (mm)	Hardness (Kg/cm^3)	Friability (%)
F1	269.6±0.20	2.76±0.16	3.8±0.5	0.23
F2	271.1±0.11	2.86±0.13	4.0±0.3	0.48
F3	270.6±0.17	2.76±0.14	3.5±0.5	0.51
F4	273.1±0.10	2.63±0.16	3.8±0.2	0.22
F5	272.0±0.19	2.68±0.15	4.0±0.5	0.35
F6	268.5±0.42	2.55±0.25	3.7±0.2	0.38
F7	269.2±0.31	2.56±0.14	3.5±0.5	0.41
F8	269.4±0.25	2.56±0.17	4.0±0.3	0.25
F9	271.3±0.13	2.48±0.14	3.5±0.1	0.28

Table No.4: Results of Drug Content

Formulations	Drug content*	Content Uniformity
F1	97.65	98.47
F2	96.53	99.59
F3	95.76	99.23
F4	98.32	98.64
F5	97.53	99.40
F6	99.16	99.46
F7	97.47	98.53
F8	98.64	98.47
F9	95.42	99.13

Table No.5: Invitro Dissolution studies

Time mins	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
60	2.8125	2.41071	4.01785	6.4285	7.2321	8.8392	4.8214	4.0178	3.2142
120	8.03883	14.4669	9.64732	15.275	13.668	18.4919	12.862	11.254	8.8428
180	18.4941	23.3223	17.6937	22.524	20.112	28.1553	20.108	18.499	20.102
240	27.354	29.7767	28.1598	33.799	28.974	33.8116	29.774	28.162	27.357
300	35.42	39.4526	37.8339	47.497	37.845	43.4919	36.235	37.033	33.015
360	45.9058	49.1392	45.108	52.371	47.53	50.7723	46.722	46.716	42.691
420	55.5995	55.6223	54.8008	58.858	57.225	61.275	53.202	54	52.382
480	62.8933	61.3089	63.7008	65.351	66.932	66.9678	60.493	63.703	61.279
540	70.9986	67.8053	70.2	71.049	75.845	79.8991	66.989	69.399	71.793
600	78.3093	75.1125	77.5098	76.752	82.358	85.6125	73.491	79.922	78.301
660	84.0209	86.4455	86.4348	81.658	88.074	91.3321	81.608	86.439	89.638
720	90.5424	92.166	94.566	87.374	96.207	99.4687	88.127	95.374	97.773

Table No.6: Standard Curve for Metformin

S.No	Concentration (µg/ml)	Absorbance (247nm)
1	5	0.15
2	7	0.20
3	9	0.26
4	11	0.32
5	13	0.37
6	15	0.43

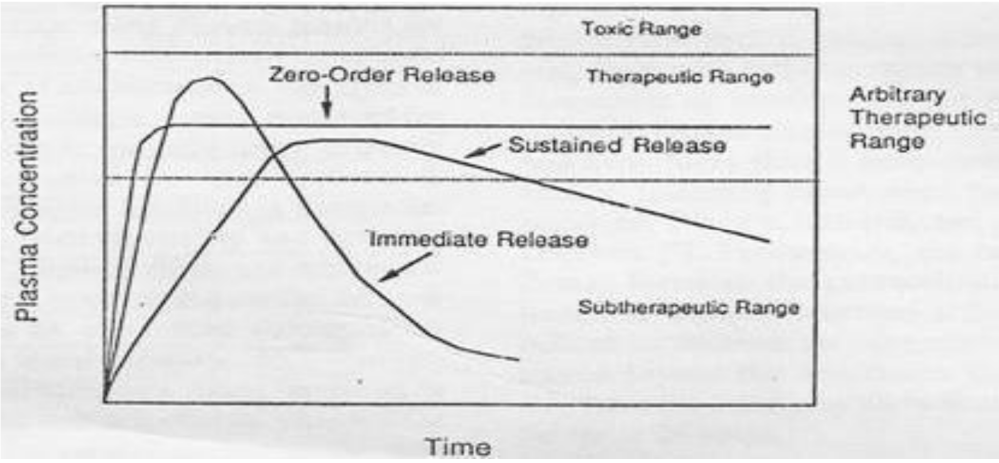

Figure No.1: Plasma concentration versus time showing differences between zero- order release, sustained release and immediate release

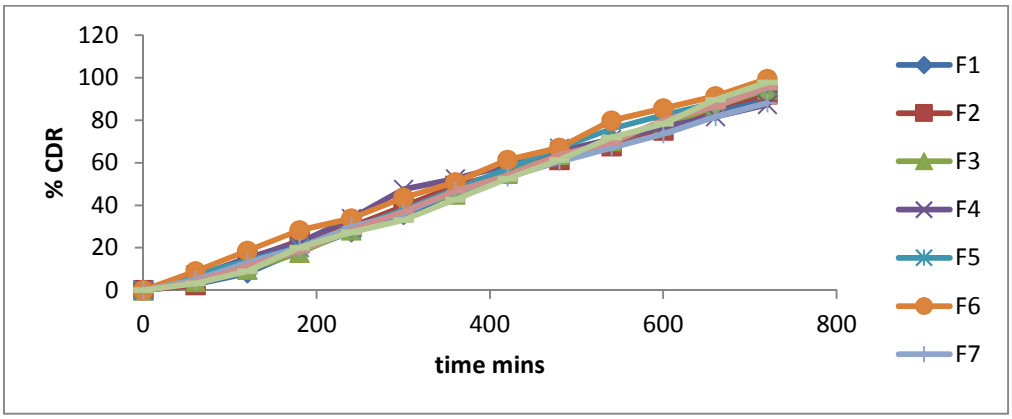

Figure No.2: Invitro drug release of all formulations

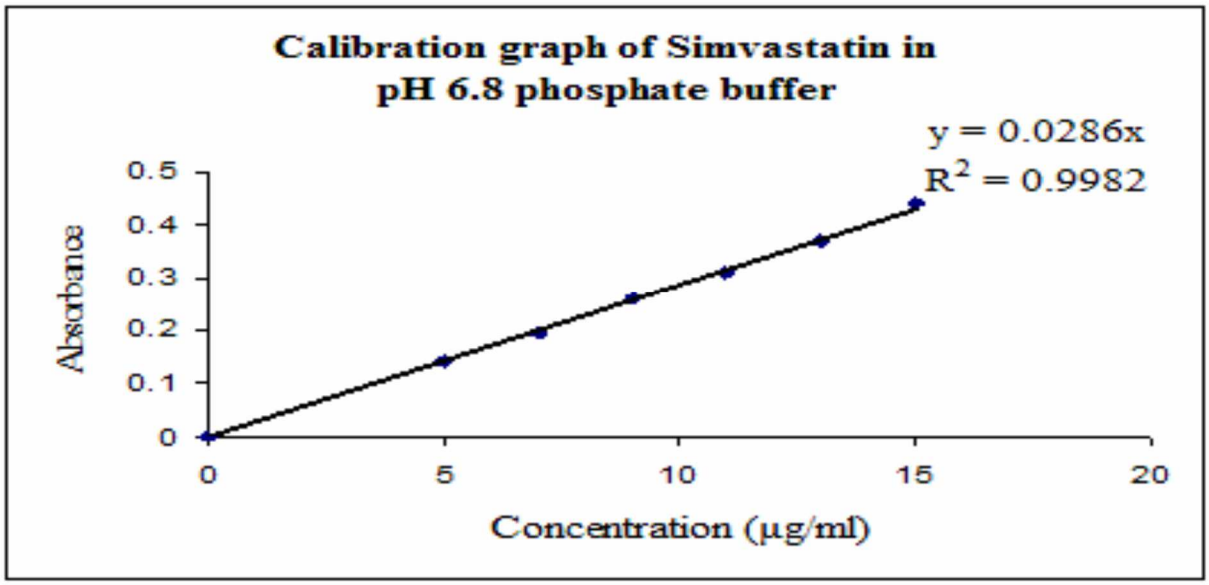

Figure No.3: Standard curve of Metformin

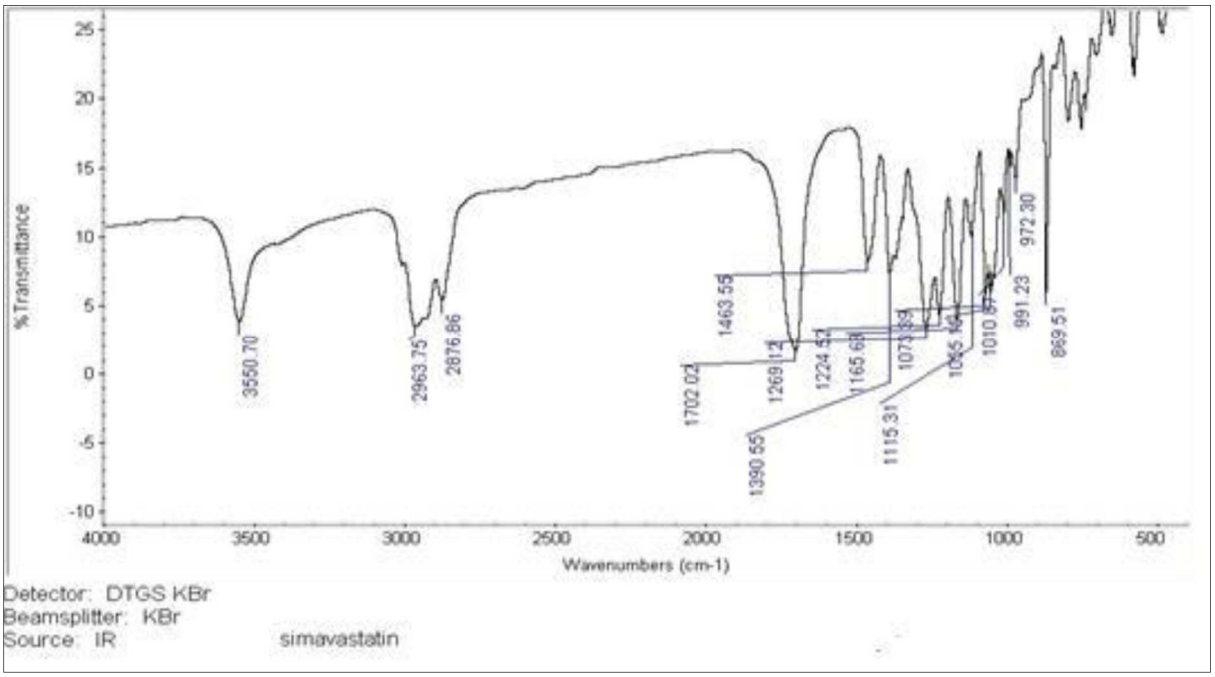

Figure No. 4: Pure Simvastatin

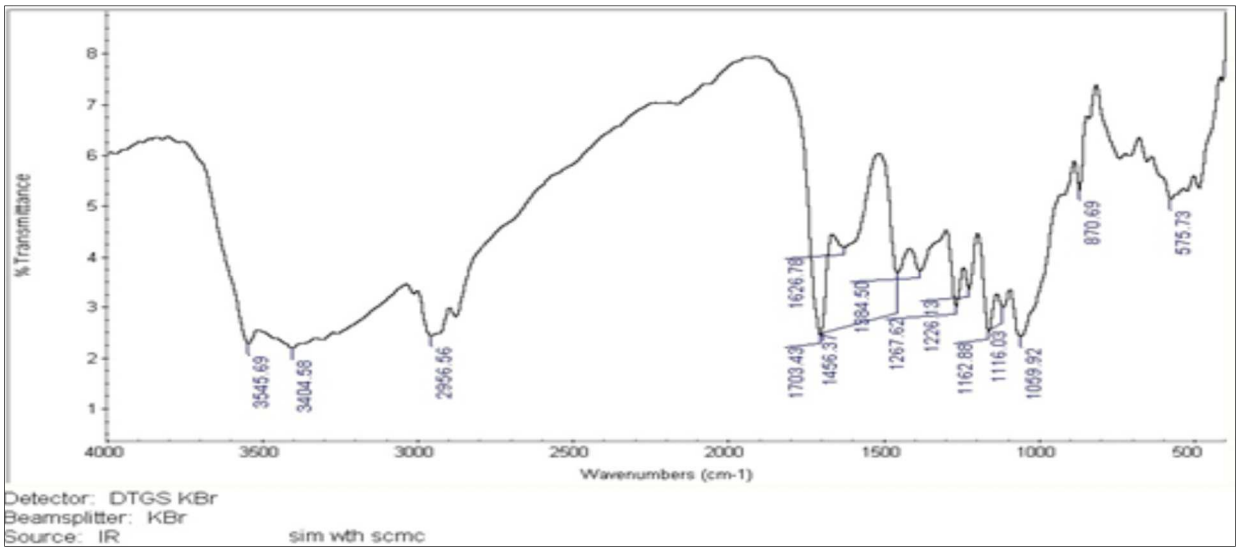

Figure No.5: Simvastatin + SCMC

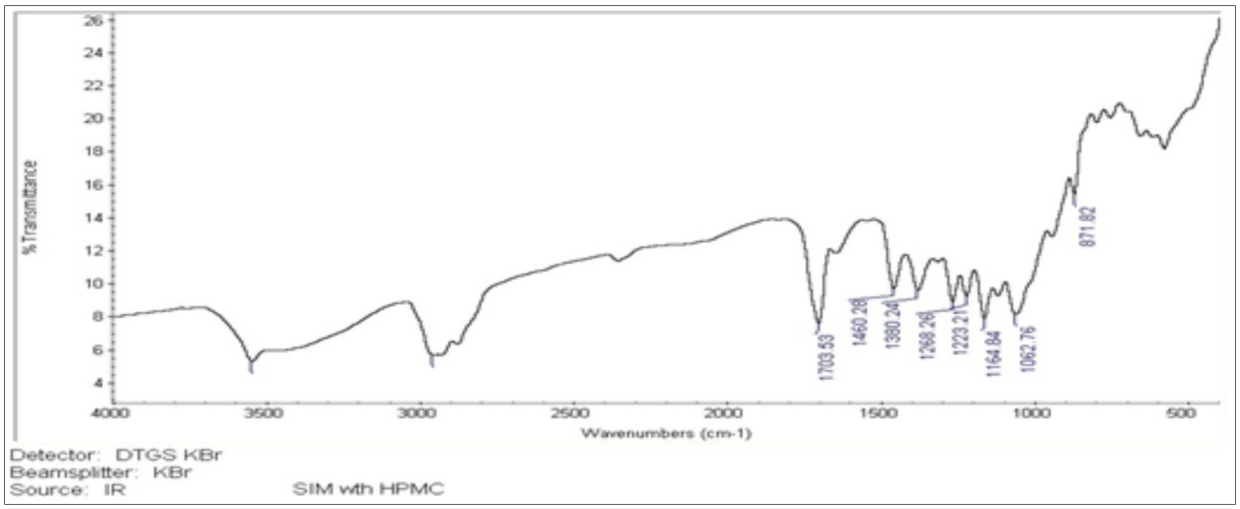

Figure No.6: Simvastatin + HPMCK4M

CONCLUSION

A satisfactory attempt was made to develop buccal drug delivery system of Simvastatin and evaluate it. The aim of Present work was to prepare extended release tablets of novel anti hyperlipidemic drug. From the reproducibility results obtained in executed experiments, it can be concluded that:

1. HPMCK4M and Sodium Carboxy Methyl Cellulose were selected to control the release of drug from the matrix system.
2. The batches were formulated and checked for all the related parameters.
3. The drug release followed Anomalous Fickian diffusion; which indicates a coupling of diffusion and erosion mechanism.

4. The batches were formulated and checked for all the related parameters and release obtained for each formulation was compared.
5. The drug content in the F6 had showed 99.46% and also the good content uniformity of 99.16%.
6. Final batch F06 was selected for accelerated stability study and kinetic modelling for drug release.
7. The drug release followed by zero order with diffusion mechanism.
8. The formulation was stable after 3 months of stability study.
9. Formulation F06 has successfully sustained release of Simvastatin in buccal cavity with great mucoadhesive strength.
10. It can be concluded that formulation F06 could be used to release the drug unidirectional in buccal cavity without the risk of mucosal irritation.

Based on the all experimental results it can be concluded that 30%SCMC and
20%HPMC K4M containing buccal formulation would be the suitable candidate for mucoadhesive drug delivery of Simvastatin with Sustained release properties for the treatment of hyperlipidemia. The 40% ethyl cellulose which is used in formulation for applying unidirectional release showed desired results.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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