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Original Article

Formulation, optimization and evaluation of buccoadhesive delivery system of lovastatin

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ABSTRACT

Lovastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme a reductase (HMG-Co A reductase). The drug undergoes extensive first-pass metabolism with less than 5% of a dose reaching circulation. In the present study, Lovastatin buccoadhesive films were prepared using HPMC 15cPs, Carbopol 934P and Poly vinyl alcohol. The patches were evaluated for their thickness, folding endurance, and weight uniformity, content uniformity, swelling behaviour, mucoadhesive strength and surface pH. *In vitro* release studies were conducted for films in phosphate buffer (pH, 6.8) containing 2% SLS solution. The patches exhibited drug release in the range of 79.51% to 99.47% in 8 hours. Data of *in vitro* release from patches were fitted into kinetic models (Higuchi and Korsmeyer-Peppas models) to explain release profiles. The optimized formulation (Film F2) showed first order release followed by zero order. The results showed that buccal films of Lovastatin improves bioavailability and can be used as a potential drug delivery system in treatment of hypercholesterolemia.

Keywords: Lovastatin, Buccoadhesive Films, In vitro release, Stability Studies.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to both the patient and the clinician . However, oral administration of drugs have disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins.[1] Consequently, other absorptive mucosa are considered as potential sites for drug administration. Trans mucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over administration for systemic drug delivery. These advantages include

- Possible bypass of first pass effect and higher bioavailability,
- Avoidance of degradation of sensitive drugs within the gastrointestinal tract,
- Avoidance of gastric irritation, and
- Depending on the drug, a better enzymatic flora for drug absorption.

Among the various Trans mucosal route, buccal mucosa has excellent accessibility, an expanse of smooth muscles and relatively immobile mucosa, hence suitable for administration of retentive dosage form. The oral cavity has rich blood supply that drains directly into the jugular vein and bypassing the liver. Direct access to the systemic circulation through internal jugular vein (buccal mucosa) bypasses drugs from hepatic first pass metabolism, leading to high bioavailability[2]. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery.

Lovastatin is an inhibitor of HMG-CoA reductase, an enzyme which catalyzes the conversion of HMG- CoA to Mevalonate. Mevalonate is a building block for cholesterol biosynthesis and lovastatin interferes with its production by acting as a competitive inhibitor for HMG-CoA which binds to the HMG-CoA reductase. Because of its hypolipidemic action, it has been used for the prevention of myocardial infarction and stroke in patients, who have symptomatic atherosclerotic diseases. It is also used for primary prevention of arterial diseases in patients who are at high risk, because of elevated serum cholesterol levels. It is used to lower serum cholesterol in patients with hypercholesterolaemia. Orally administered lovastatin undergoes high first pass metabolism in the gut wall and liver and the bioavailability is only about 5-15%[3]. Hence there is need to develop drug delivery systems, which can overcome the first pass effect and this work is aimed to prepare a buccal dosage form of lovastatin bioavailability. This study aims to formulate Buccoadhesive films of Lovastatin using HPMC 15cPs, carbopol 934P

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and PVA, as polymers in order to provide the film with bioadhesive property and to modify the rate of drug release.It also aims at Characterization of the formulated films for Physico-Chemical properties and release pattern.

MATERIALS AND METHODS

Materials: Lovastatin was obtained as a gift sample (Sterling biotech Ltd,Gujarat), Carbopol 934P and hydroxy-propyl- methylcellulose 15cPs (HPMC 15cPs)and PVA were obtained from S-d fine chemicals. Other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India),Bengal chemicals and Pharmaceuticals and Nice Chemicals.

Preparation of Films: Buccoadhesive Films of Lovastatin were prepared by solvent casting technique[4] using film forming polymers mentioned in table.1. HPMC and Carobol were weighed in the required quantity and dissolved in 2:1 mixture of ethanol and deionized water. PVA was dissolved in deionized water by heating. The two solutions were mixed. One drop of glycerol was added as plasticizer. Appropriate quantity of lovastatin was weighed and dispered in the polymer solution. The solution was transferred to a glass petridish of diameter 5cm, and dried for 48 hours

Evaluation of the Films

***Thickness uniformity of the patches*:** Three patches of each formulation were taken and the patch thickness was measured using micrometer screw gauge at three different places and the mean value was calculated[5]

Folding endurance: Folding endurance was determined by repeatedly folding a small strip of film at the same place, till it brokes. The mean value was calculated[6].

Swelling studies: 1 cm^2 films were weighed. They were allowed to swell on the surface of agar plate maintained at 37 ± 0.2ºC. Increase in the weight of patch after1 hour was noted. Percent swelling was calculated.

$\% S = (x_t - x_o) / x_o \times 100$

X_t = weight of swollen patch after 1 hour.

X_o = Initial weight.

Absolute drug content: 1cm^2 films were put in 100ml pH 6.8 phosphate buffer containing 2% SLS[7]. Shaken continuously for 24 hours. Then the whole solution was filtered. The absorbance of the solution was determined in a spectrophotometer (Jasco v-630) at wavelength of 238nm[3] after proper dilution and drug content was determined.

***Ex – vivo* bioadhesion test:** Fresh goat buccal mucosa was separated and washed with phosphate buffer. Tied to the mouth of a beaker (25ml), filled with 6.8 pH buffer. A rubber stopper is fixed to the bottom of right pan of a physical balance. Another rubber stopper, added to right pan to adjust the weight. Prepared film was stuck to lower side of rubber stopper with Cyano acrylate adhesive. A small beaker of 50 ml was placed in the left pan. Again weight balanced. The balance is kept in contact with film for 5 minutes. Water was slowly added using a burette, till the patch was detached from the mucosal surface. The weight required to detach, provided the measure of mucoadhesive strength[8].

***Ex – vivo* mucoadhesion time:** Freshly cut buccal mucosa of goat is adhered to a glass slide. Film was wetted with one drop phosphate buffer and applied to the mucosa for 30 seconds. The glass slide is them put in beaker, filled with 200ml phosphate buffer of pH 6.8. After 2 minutes, a 50rpm stirring rate is applied to simulate buccal environment and patch adhesion monitored.

***In- vitro* release studies:** The USP rotating paddle method was used to study the drug release from buccal patches. The dissolution medium consisted of 250 ml of phosphate buffer containing 2 % SLS. The release was performed at 37 ± 0.5ºC, at a rotation speed of 50rpm. One side of the buccal patch was attached to a glass slide with cyanoacrylate adhesive. It was put in the dissolution vessel, so that the patch remained on the upper side, of the disk. 1 ml samples were withdrawn at predetermined time intervals (0.25, 0.5, 1, 2, 4, and 8 hours) and replaced with fresh medium. Samples were filtered, diluted and analyzed spectrophotometrically (JASCO V-630) at a fixed wave length of 238 nm[3].

***Ex – vivo* buccal permeation:** The ex- vivo permeation through goat buccal mucosa[9] was performed using a Franz type glass diffusion cell at 37 ± 0.2ºC. Goat buccal mucosa was obtained from slaughter house. Buccal mucosa was mounted on the diffusion cell, filled with 6.8 pH phosphate buffer containing 2% SLS. 50 rpm stirring was applied. 1 ml samples were withdrawn at predetermined time intervals (0.25, 0.5, 1, 2,3, 4, 6 and 8 hour) and analyzed for drug content at 238 nm.

***In – vivo* studies:** All *in- vivo* studies in rabbits were carried out after obtaining permission from institutional Animal ethics committee.

Pharmacokinetic studies: The required number of healthy albino rabbits weighing between 2-2.5 k.g were fasted overnight but provided with water ad-libitum. The animals were restrained in a restraining cage. They were anesthetized in order to administer the buccal patch. 6 healthy albino rabbits were selected for the study. 1cm^2 buccal patch containing the drug was placed in the buccal cavity of 2 rabbits. To ensure a unidirectional drug release a backing layer of ethyl cellulose was adhered to the film using cyano acrylate adhesive.

Another 2 were administered Lovastatin tablets (ELSTIN 10mg) using a feeding tube. 1 ml blood samples were withdrawn from marginal ear vein, at predetermined time intervals (0,0.5, 1, 2,3, 4, 6, 8,10 and 12 hours). Serum was separated, and analyzed by U.V spectrophotometry.[10,11]

***In vitro-in vivo* correlation (IVIVC):** Serum drug concentration was calculated from the peak area for the *in vivo* samples using the calibration curve prepared for the drug in serum. Lovastatin serum levels were converted to the percentage lovastatin absorbed by the use of modified Wagner-Nelson equation for the single compartment model as follows:

$$\% \text{ absorbed} = \frac{C_{(t)}/K_{el} + AUC_{0\rightarrow t}}{AUC_{0\rightarrow inf}} \times 100$$

Where C_t is the serum concentration at time t, K is the elimination rate constant, $AUC_{0\text{-}t}$ is the area under the curve from 0 to time t and $AUC_{0\text{-}\infty}$ is the area under the curve from 0 to infinity. The *in vivo* absorption values were related directly to the *in vitro* dissolution data to complete the IVIVC[12]. The pharmacokinetic parameters were determined using Win Lin software (Cole-Parmer Instrument Co., Chicago, IL, USA). The % drug absorbed *in vivo* (Y-axis) was plotted with the % drug released *in vitro* (X-axis) which were obtained from the dissolution of the formulation. The percentage drug released *in vitro* (x-axis) was plotted against the percentage absorbed *in vivo* (y-axis).

Accelerated stability studies: According to ICH Q1A(R2) guidelines for drug products intended to be stored at room temperature, the accelerated stability studies are to be carried out at controlled temperature and humidity conditions of 40 ± 2ºC and humidity of 75 ± 5% RH.[13] Thus for the stability evaluation of the buccoadhesive patches the samples were stored at a temperature of 40 ± 2ºC and humidity of 75 ± 5% RH. The samples were withdrawn at 0, 30, 60 and 90 days and the physical characteristics and drug content were determined. The zero time samples were used as controls.

The samples were evaluated for the following parameters:

1. **Weight gain/loss:** Three buccoadhesive patches were withdrawn at regular intervals of time and were weighed individually and the average weight of the patches were also determined. Any gain/loss in the weight from the initial weight was noted.
2. **Bioadhesive Strength:** Three buccoadhesive patches were withdrawn at regular intervals of time and bioadhesive strength was determined.
3. **Surface pH:** Three buccoadhesive patches were withdrawn at regular intervals of time and the surface pH was determined.
4. **Folding endurance:** Three buccoadhesive patches were withdrawn at regular intervals of time and the folding endurance was determined.
5. **Similarity factor:** The in vitro drug release profile of the samples subjected to accelerated stability studies were compared using similarity factor (f_2). A f_2 value of 50-100 indicates that the dissolution profiles are similar.
6. **Drug content:** Three buccoadhesive patches were withdrawn at regular intervals of time and were analyzed for drug content.

The data for surface pH, % weight gain/loss, mucoadhesive strength and folding endurance were analysed for statistical significance by Student's t-test with statistical significance set at $p < 0.05$ using GraphPad Instat software (GraphPad Software Inc., CA, USA).

RESULTS AND DISCUSSION

Drug Polymer Compatibility Studies: FTIR spectra of physical mixture was compared with FTIR spectra of pure samples(Fig.1), FTIR spectra of mixture showed all the relevant peaks of individual components. All the characteristics peaks of Lovastatin were present in the spectra thus indicating compatibility between the drugs and polymers which confirmed that there were no significant changes in the chemical integrity of the drug

Optimization of film

Optimization was done on the basis of evaluation of physical properties and in-vitro release pattern.Film F2 (Fig.3) was considered to be the optimized formulation on the basis of its physical characteristics (Tab.2) and in vitro release pattern. It gave the maximum drug release in *in-vitro* release studies (Fig.2). The Scanning Electron Microscope images of f2 are presented in figure 4.

Kinetics of drug release: To analyze the in-vitro release data, various kinetic models were used to describe the release kinetics. The following plots were made : Cumulative % drug release vs time (zero order kinetic model); log cumulative of % drug remaining vs time (first order kinetic model); cumulative % drug release vs. square root of time (Higuchi model); log cumulative % drug release vs. log time (korsmeyer model).These are presented as figures 5,6,7 and 8. The optimized formulation (Film F2) showed first order release followed by zero order. The release data when analysed using Higuchi model and Korsmeyer – Peppas model

indicated that diffusion is the predominant process of drug release along with polymer erosion.

***Ex-Vivo* buccal permeation study:** The buccal permeation study of Optimized formulation f2 was performed in a Franz diffusion cell. A total of about 63% permeation of the drug was observed on 8 hours of study.The results are presented in Table.3.The formulation showed acceptable permeation in diffusion study using goat buccal mucosa.

***In-vivo* studies**

Preparation of calibration curve of lovastatin in plasma: A primary stock solution of 1 mg/ml of lovastatin was prepared and diluted with methanol to produce 100, 200, 300, 400 and 500 mg/ml concentration.

Extraction of lovstatin from serum: The procedure is modified from the extraction and estimation of lovstatin described by K. Gupta, et al[11]. 0.9 ml of serum was spiked with 0.1 ml of the 100 µg/ml standard solution. 1.5 ml of 10% Trichloro acetic acid solution was added as protein precipitating agent and centrifuged for 15 min. The supernatant was transferred to another test tube to which 1 ml of 1 N NaOH was added. The drug was extracted using ethyl acetate (5ml x 2), and the organic layer containing the drug was separated and evaporated to dryness. The residue was reconstituted in 5ml methanol and analysed using Jasco V-630 UV spectrophotometer at 238 nm. Table.4. shows data of prepared calibration curve of lovatatin in plasma.Figure10 shows serum drug concentration v/s time profiles of f2 and oral tablet of Lovastatin.

***In-vitro – in vivo* correlation: C**arried out using the Wagner – Nelson method. Percentage drug released is plotted against percentage drug absorbed (Fig.11). A correlation coefficient (r^2) value of 0.9949 indicated an excellent *in vitro-in vivo* correlation

Accelerated stability studies: The stability studies were conducted in a stability chamber for a period of 3 months. The patches were seen to change colour to light yellow after 60 days. The colour did not intensify later. Other physical properties were affected marginally.Results are presented in table 5.Apart from colour change the formulation retained all its initial properties,which shows that the formulation exhibited good stability during the period of study.

CONCLUSION

A 1:2 ratio of HPMC and carbopol was inferred to be the optimum concentration for the formation of an inter polymer complex. The optimized film was translucent with a moderately smooth surface. It was uniform in terms of thickness, weight and absolute drug content. The surface pH and swelling properties were within acceptable limits. It was observed that the exposure of the films to aqueous medium caused neither rupture nor rapid erosion. The *in-vitro* residence time and *ex-vivo* mucoadhesive strength ensured that the system will not get dislodged during the treatment period. Cumulative drug release data showed sustained release of the drug up to a maximum of 99% in 8 hours. The release data when analysed using Higuchi model and Korsmeyer – Peppas model indicated that diffusion is the predominant process of drug release along with polymer erosion. In short, the formulation was found ideal in terms of swelling, mucoadhesive properties, mechanical properties and in vitro drug release. The ex-vivo permeation study showed a maximum of about 63% permeation in 8 hours. . A higher bioavailability of the drug was observed compared to an oral tablet, probably due to circumventing first pass metabolism. The results indicated that Buccoadhesive formulations of Lovastatin could be utilized as potential delivery system for the treatment of cardiovascular disease.

Table.1: Composition of Buccal films

Formulation	Polymer ratio	HPMC (mg)	Carbopol (mg)	PVA (mg)	Lovastatin (mg)
F1	1:1	200	200	100	200
F2	1:2	134	266	100	200
F3	2:1	266	134	100	200
F4	2:3	160	240	100	200
F5	3:2	240	160	100	200
F6	1:4	80	320	100	200
F7	4:1	320	80	100	200

Table.2. Comparison between different formulations.

Weight variation	**24.1±0.008**	**25.6±0.005**	**23.9±0.009**	**25.4±0.005**	**22.2±0.014**	**24.61±0.012**	**25.1±0.026**
Patch thickness	**parameter**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Percent swelling	**30.16 ± 1.79**	**29.39 ± 1.28**	**32.13 ± 1.79**	**29.17 ± 1.05**	**30.42 ± 1.52**	**25.21 ± 1.63**	**33.85 ± 1.07**
Force of adhesion	**0.123**	**0.148**	**0.116**	**0.141**	**0.117**	**0.199**	**0.106**
pH	**6.77**	**6.75**	**6.60**	**6.81**	**6.57**	**6.14**	**6.71**
Folding endurance	**>300**	**>300**	**>300**	**>300**	**>300**	**>300**	**>300**
Mucoadhesive time(hr)	**>8**	**>8**	**>8**	**>8**	**>8**	**>8**	**5**
Percent drug release after 8 hours	**97.726 ± 2.105**	**99.471 ± 0.382**	**89.258 ± 3.527**	**84.416 ± 4.8703**	**87.089 ± 3.208**	**79.512 ± 1.364**	**97.113 ± 2.712**

Table.3.ex-vivo buccal permeation study

Time (min)	**Percentage of drug permeated (%)**
15	3.187
30	6.168
60	25.858
120	44.264
180	54.228
240	56.021
360	59.914
480	62.982

Table.4.Data for Calibration curve of Lovastatin

Concentration (µg/ml)	**Absorbance at 238 nm**	**R^2**
10	0.1599	0.9873
20	0.3117	
30	0.4123	
40	0.6013	
50	0.6788	

Table.5.Stability data of optimised buccoadhesive patches after storage at 40 ± 2 ºC and 75 ± 5% RH

Time (days)	**Surface pH (n=3) (± S.D.)**	**% Weight gain/ loss (n=3) (± S.D.)**	**Mucoadhesive strength (g) (n=3) (± S.D.)**	**Folding endurance (n=3)**	**Similarity factor (f_2)**	**% Drug remaining**
0	6.75 ± 0.12	0.83 ± 0.32	15.12 ± 0.17	>300	-	100
30	6.76 ± 0.14	1.09 ± 0.18	15.10 ± 0.15	>300	88.73	99.80
60	6.68 ± 0.17	1.20 ± 0.29	14.98 ± 0.11	>300	79.65	99.24
90	6.66 ± 0.15	1.26 ± 0.95	14.93 ± 0.17	>300	69.27	98.89

Figure 1: FTIR of a)Lovastatin pure b) Lovastatin with hydroxy propyl methylcellulose ,Carbopol and PVA

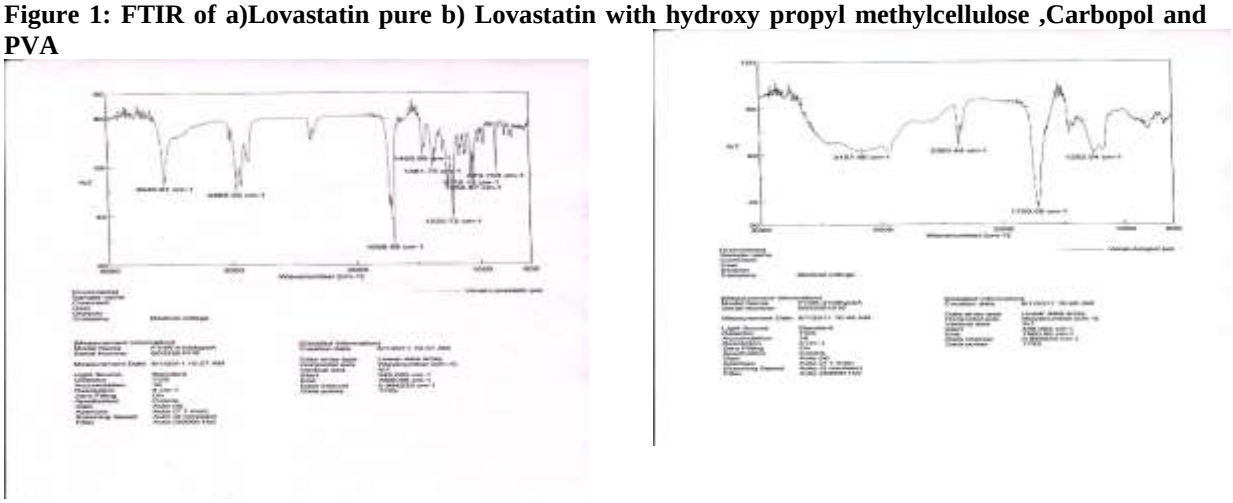


Figure.2. *In- vitro* release studies.cumulative percentage drug release vs time.

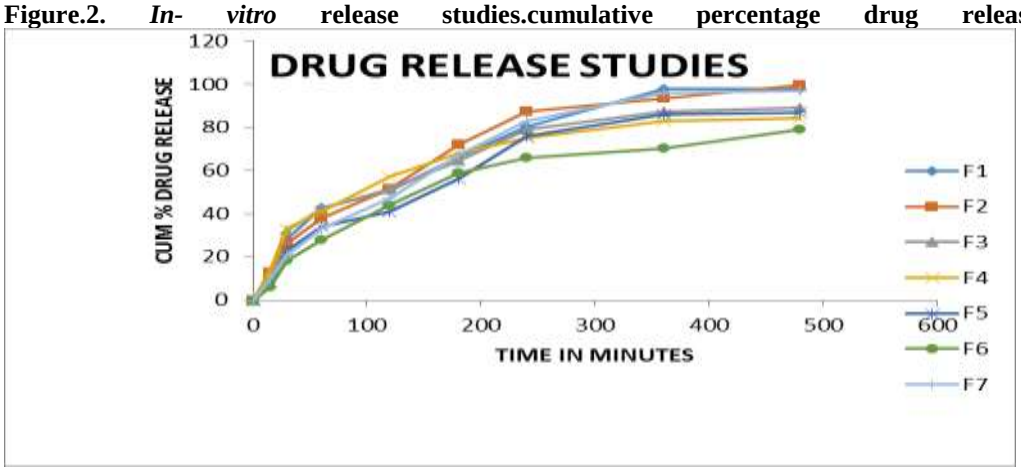


Figure.3: Photograph of F2

Figure.4. SEM IMAGES OF F2

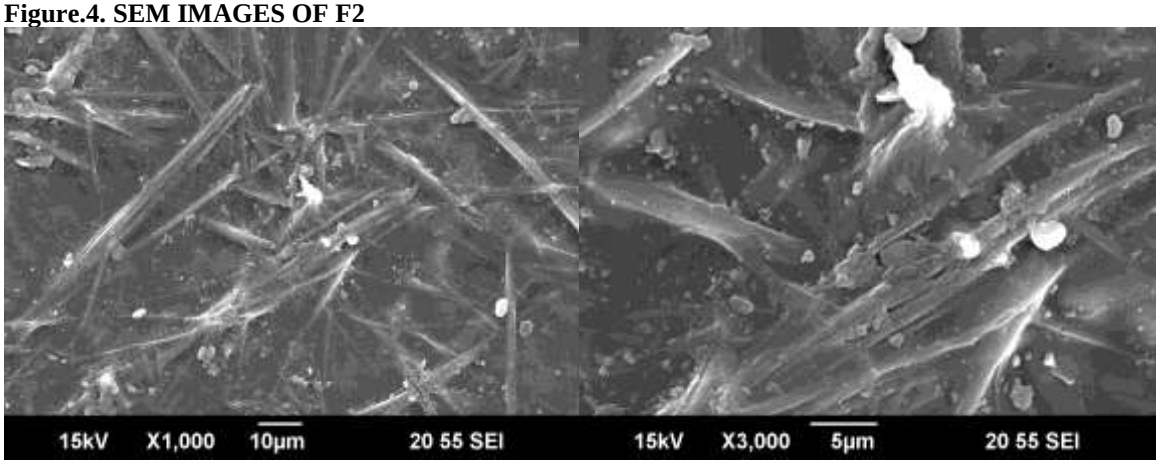


Figure.5.

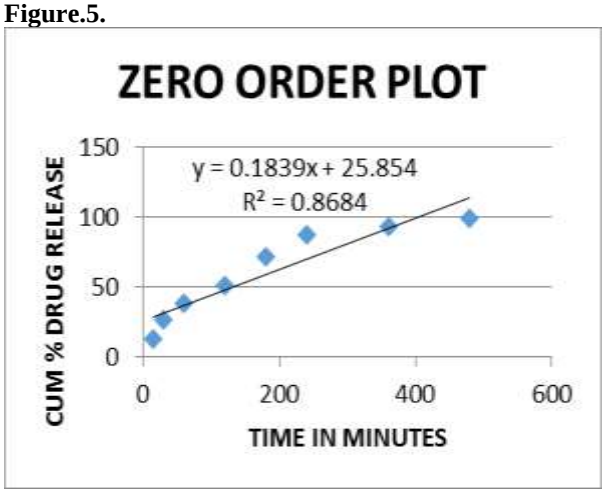


Figure.6.

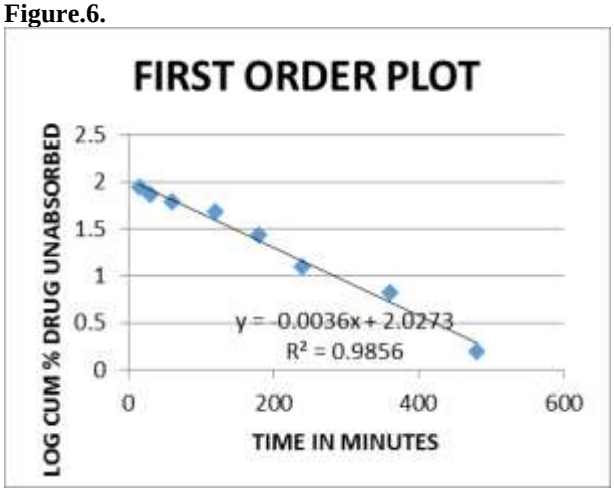


Figure.7.Higuchi Plot

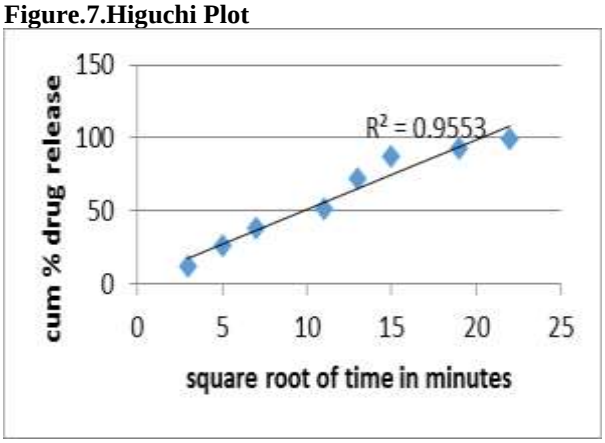


Figure.8.Korsmeyer peppas model

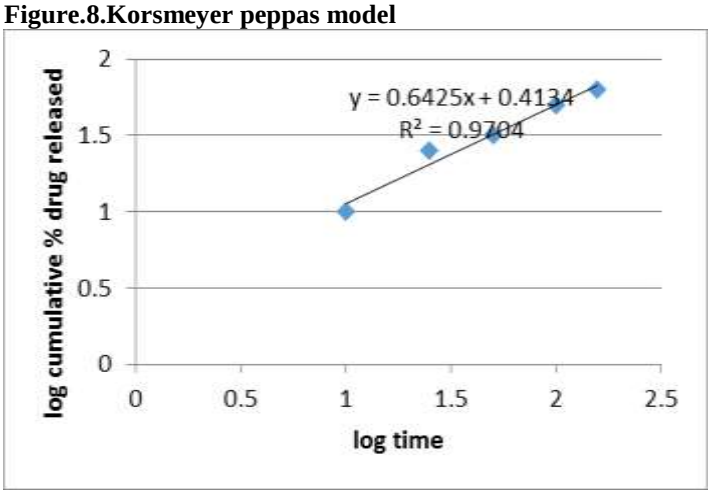


Figure.9.

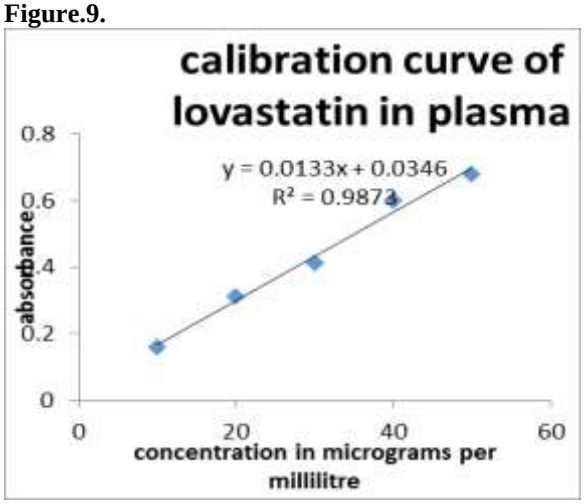


Figure.10.SERUM DRUG CONC. VS.TIME PROFILE

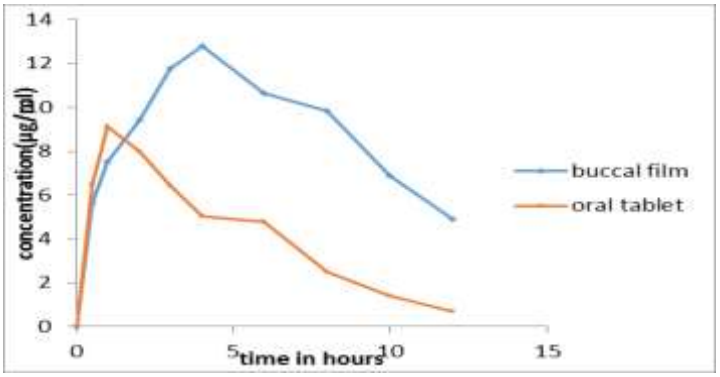
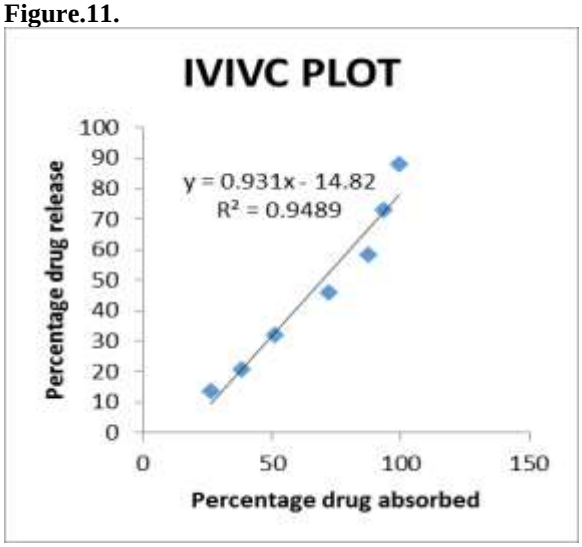


Figure.11.



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