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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF GASTRO RETENTIVE MUCOADHESIVE TABLETS OF LOVASTATIN

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ABSTRACT

The purpose of this study was to design bilayer mucoadhesive tablets of Lovastatin. Bilayer mucoadhesive tablets comprised two layers, i.e., immediate release and controlled release layers. The immediate release layer comprised sodium starch glycolate, Crospovidone and Croscarmellose sodium as super disintegrant either alone or in combination and the sustained release layer comprised Chitosan, Sodium Alginate, Carbopol 934P, Sodium CMC HPMC K4M, HPMC K15M, HPMC K100M as the release retarding and mucoadhesive polymers. Direct compression method was used for formulation of the bilayer tablets. More than 90% of lovastatin was released within 30 min from the immediate release layer. HPMC K100M retarded the release of Lovastatin from the controlled release layer for 12 h. Diffusion exponents (n) were determined for all the formulations (0.135-0.594). The release of Lovastatin was found to follow first order kinetics and Korsmeyer-Peppas model. The optimized formulation was found to have good mucoadhesive strength in sheep gastric mucosa. Therefore, biphasic drug release pattern was successfully achieved through the formulation of mucoadhesive bilayer tablets in this study.

Key Words: Gastroretentive, HPMCK100, Mucoadhesive, Bilayer tablets, Lovastatin.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration but is associated with the shortcomings of repeated dosing and fluctuations in plasma drug concentration at steady-state.

Extended release dosage forms are formulated in such manner as to provide constant or nearly constant drug levels in plasma with reduced fluctuations via slow release over an extended period of time[5]. Controlled release drug delivery systems that can be retained in stomach for long time are important for drug that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved gastrointestinal absorption of drugs with narrow absorption window as well as for controlling release of drugs having site specific absorption limitation.

Different approaches have been proposed to retain dosage form in stomach. These include bioadhesive or mucoadhesive systems, swelling and expanding systems, floating systems, and other delayed gastric emptying devices (Asma Afroz *et al*., 2011).

The concept of mucoadhesion was introduced into controlled drug delivery in the early 1980s. Mucoadhesion is the attachment of a natural or synthetic polymer to a biological substrate. It is an important new aspect of controlled drug delivery. There has been increased interest in recent years in using mucoadhesive polymers for drug delivery. Substantial effort has recently been focused on placing a drug or a formulation in a particular region of the body for extended periods of time. This is needed not only for targeting of drugs but also to better control of systemic

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drug delivery. The biphasic system is used mostly when maximum relief needs to be achieved quickly followed by a sustained release phase. It also avoids repeated administration of drug and may contain one or two drugs for immediate release and sustained release layer (Anusha *et al*., 2013).

Lovastatin, a HMG Co-A reductase inhibitor, highly lipophilic but poorly water soluble drug belonging to the class statins, widely used for the treatment of hypercholesterolemia and so preventing cardiovascular disease. Its biological half-life is 1.1– 1.7 hr, which is relatively short with an oral bioavailability of 5%. Patients are advised to take Lovastatin in divided daily doses. The present study was undertaken to prepare bilayer tablets of lovastatin containing an immediate release layer and mucoadhesive extended release layer to provide a consistent dosage through sustaining an appropriate level of the drug over time and enhance the bioavailability of Lovastatin. (Ajit Kulkarni *et al*., 2009; Karthik Neduri *et al*., 2013)

MATERIALS AND METHODS

Materials

The drug (Lovastatin USP grade), Crospovidone (CP), Sodium Starch Glycholate (SSG), Croscarmellose sodium(CCS) Chitosan, Sodium Alginate, Carbopol 934P, Sod.CMC HPMC K4M, HPMC K15M, HPMC K100M.

Formulation of bilayer mucoadhesive tablet of Lovastatin

Bilayer mucoadhesive tablets contain two layers i.e. immediate release layer and mucoadhesive sustained release layer.

Optimization of immediate release (IR) layer

The immediate release layer was prepared by blending the drug with different concentrations of super-disintegrating agent (Crospovidone, SSG, Croscarmellose sodium) either alone or in combination and other excipients, Micro- crystalline cellulose, magnesium stearate and talc. The physical mixture then compressed by direct compression method for preliminary studies to optimize the immediate release formulation using 8mm concave punch .Nine formulations were made in order to achieve desired disintegration time.

Formulation of mucoadhesive sustained release (SR) layer

The mucoadhesive SR layer prepared by weighing required quantities of drug, polymer(Chitosan, Sodium Alginate, Carbopol 934p, Sod.CMC HPMC K4M, HPMC K15M, HPMC K100M), and passing through #40 mesh and mixing in a poly bag for about 5-10 min and taken into a mortar. To that mixture Micro crystalline cellulose, Magnesium stearate, talc were added and mixed thoroughly. Formulation composition of all batches given in the Table 2.

Preparation of bilayer tablet

Bilayer mucoadhesive tablets (BF) were prepared by direct compression method using 8mm punch. First the mixture of SR layer was poured into the die cavity and compressed. Then the upper punch lifted and punches are drawn back to the feed place and contents of immediate release layer were placed in thedie cavity over the SR layer tablet and compressed with optimum compression strength to produce bilayer mucoadhesive tablets.

Drug - Excipients compatibility study

Compatibility between the drug and polymer was studied using FTIR. FTIR analysis was done on SHIMADZU FT-IR Spectrophotometer. Five mg of substance was taken on Agate Pestle. It was thoroughly titrated with 100mg of Potassium Bromide. A pellet/disc was made out of the mixture and introduced in the instrument. Resolution of 4cm-1, scanning was done in the range of 500 - 4000 cm-1. Results are shown in Fig. 1-3.

Disintegration time: One immediate release tablet formulation was placed in each of six tubes of disintegration test apparatus. Time required for complete disintegration of tablet fragments through sieve (#10) was considered as a disintegration time of tablet.

In- Vitro disintegration time was performed at 50 rpm. 0.1N HCl, pH 1.2, 900 ml was used as disintegration medium, and the temperature of which maintained at 37±2oC and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Evaluation of Bilayer Tablets

Post formulation studies: The tablets of the proposed formulations (BF1 to BF16) were evaluated for hardness (Kg/cm2) (using Monsanto hardness tester), weight variation (mean ±SD), thickness (mm) (using Vernier calipers), friability ((Roche type friabilator) FT1020 (ver.2) Labindia) at 25 rpm for 4 min and drug content.

Uniformity of drug content: An accurately weighed amount of the tablet powder was dissolved in methanol and volume was made to 100 ml. The solution was filtered through a Whatmann filter paper No. 41. An aliquot of 1 ml was taken and diluted to 100 ml with methanol. Absorbance of the solution was taken using UV visible spectrophotometer at 238nm.

Lovastatin Tablets should contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of lovastatin ($C_{24}H_{36}O_5$).

In vitro dissolution studies

In vitro dissolution studies were carried out in USPXXIV tablet dissolution test apparatus-II (Lab India), employing a paddle stirrer at 50 rpm using 900ml of 0.1N HCl at 37±0.5ºC as dissolution medium. One tablet was used in each test. At predetermined time intervals 5ml of

the samples were withdrawn by means of a syringe fitted with a prefilter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 238 nm using UV-Visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicate.

Model dependent approach

The results of *In vitro* release profiles obtained for all the BF tablet formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).

$Q = Q_0 – K_0 t$

2. Log cumulative percent drug remaining versus time(First-order kinetic model).

$\ln Q = \ln Q_0 – K_0 t$

3. Cumulative percent drug released versus square root of time (Higuchi's model).

$Q = K \sqrt{t}$

4. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

$Q = K_2 t$

Swelling Index

Tablet matrices were placed in the dissolution test apparatus in 900 ml 0.1N HCL at 37± 0.5°C. At time interval of 2, 4, 6, 8, 10, 12 hours tablets were removed from buffer medium and excess water on their surface was carefully blotted with filter paper. Percentage swelling (swelling index) was calculated by using the formula:

$$\text{Swelling index} = \frac{W1 - W2}{W2} \times 100$$

Ex-vivo measurement of mucoadhesive strength: Mucoadhesion strength of the tablet was measured on a modified physical balance using Goat stomach mucosa as a model membrane and buffer media 0.1N HCl (pH 1.2) was used as moistening fluid. The goat stomach mucosa was obtained from local slaughter house. The underlying mucous membrane was separated carefully using surgical blade and washed thoroughly with 0.1N HCl (pH 1.2). It was then tied over the glass arrangement using a thread.

A double beam physical balance was taken and to the left arm of balance a thick thread of suitable length was hanged and to the bottom side of thread a glass stopper with uniform surface was tied. The beaker was filled with 0.1N HCl (pH 1.2) up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The tablet was then stuck to glass stopper from one side membrane using a cyanoacrylate adhesive (Feviquick).

The two sides of the balance were made equal before the study, by keeping a weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the glass stopper along with the tablet over the mucosal membrane with a weight of 5 g. The balance was kept in this position for 3 min. Then, the weights were increased on the right pan until tablet just separated from mucosal membrane. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength. The mean value of three trials was taken for each set of formulations. After calculating mucoadhesion strength the force of adhesion and bond strength parameters were calculated from following equations as;

$$\text{Force of Adhesion } (N) = \text{Mucoadhesive strength} \times 9.8/1000$$

$$\text{Bond Strength } (N/m^2) = \text{Force of Adhesion}/\text{Surface Area.}$$

RESULTS AND DISCUSSION

Drug-excipients compatibility study

The FTIR spectra of pure lovastatin and optimized formulation Fig1-Fig 3 exhibited peaks at3540.41 cm-1, 2929.30 due methyl and methylene C-H stretching, 1725.98 cm-1Carbonyl Stretching, 1261.49cm-1,1055.1cm-1 due to lactone and ester C-O-C bending vibration stretching. Peak broadening was observed with optimized SR formulation which could be due to excessive hydrogen bonding. Incorporation of Lovastatin with Superdisintegrants in IR formulation didn't change the nature of its functional groups. Thus, confirms the structure of Lovastatin drug.

Selection of optimized immediate release (IR) layer: The immediate release layer of the bilayer tablets disintegrated, and liberated Lovastatin. The in- vitro disintegration time (DT) of the tablets was found to being the range of 20-47 sec. Tablets containing combination of SSG-CCS (IF5) SSG-CP(IF7), CCS-CP(IF9) had disintegration time of 27±1,20±1,24±2sec respectively. All the tablets had disintegration time less than 60 sec. From the results of the dissolution rate of all the formulations, it is demonstrated that, the bilayer tablets could be prepared by using combination of Superdisintegrants SSG and CP (DT 20 sec). Hence, the formulation IF7 was used for the formulation of bilayer mucoadhesive tablet.

Preformulation studies: The loose bulk density and tapped bulk density of all the batches were varied from 0.363±0.030 to 0.706±0.006g/ml and 0.432±0.012 to 0.887±0.010 g/ml.

Carr's consolidation index ranged from 12.39±0.001to 20.87±0.005. Results clearly showed that flow- ability of all the formulations is good and has good compressibility.

Post formulation studies: The tablets of the proposed formulations (BF1 to BF5) were evaluated for hardness, weight variation, thickness, friability and drug content.

The thickness for tablets (mean ± SD) ranged from4.85 ± 0.04 to 5.07 ± 0.02mm.The hardness and Friability (mean ± SD) of the tablets was found to be ranging from 5.2±0.20 to 5.9±0.20 kg/cm^2 respectively. All the tablets passed the weight variation test i.e., they were within the Pharmacopoeia limits of ±5%. Content uniformity ranged from 98.80±0.54to 100.47±0.34. The tablet meets the USP specification of (90-110%)

As such it can be concluded that, all the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content.

In-vitro drug release

From the Figure 4, formulation BF1-BF5, BF 2 showed rapid burst release within 3-4hrs. Formulation BF2, sustained the drug release up to 12 hrs. BF2 was selected as optimized formulation since it released maximum amount of the drug in 12 hrs compared to others. The mechanism of drug release from BF2 was found to be Fickian diffusion as evident from release exponent (n) value.

Swelling characteristics

The % swelling index of the formulations BF1 to BF5 ranges from 54.36±0.16 to 152.52±0.73.00% (25% of HPMC K100M) shown in Fig. 5. The percentage water up take was found to be improved by increased concentration of HPMC in formulation. The viscosity of the polymer (HPMC K4M, HPMC K15M, HPMC K100M and Carbopol 934P) had major influence on swelling process, matrix integrity, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Mucoadhesive strength

The values of Mucoadhesive strength (Fig:6) indicate that the bioadhesive force increased significantly as the concentration of Mucoadhesive polymer increased.

Table 1. Composition of Immediate release layer (150mg)

Formulation Code	Drug	Sodium starch glycolate	Croscarmellose Sodium	Crospovidone	Aerosil	Mg.stearate	MCC
IF1	10	10	-	-	5	5	120
IF2	10	-	10	-	5	5	120
IF3	10	-		10	5	5	120
IF4	10	5	5	-	5	5	120
IF5	10	20	20	-	5	5	110
IF6	10	5	-	5	5	5	120
IF7	10	20	-	20	5	5	110
IF8	10	-	5	5	5	5	120
IF9	10	-	20	20	5	5	110

*All the quantities are weighed in mg

Table 2. Composition of Sustained release layer (200mg)

Formulation	Drug	Na. Alginate	Chitosan	Carbopol 934P	HPMC K4M	HPMC K15 M	HPMC K100 M	Sod.CMC	Talc	Mg. Stearate	MCC
BF 1	50	-	-	-	-	-	25	-	3	3	119
BF 2	50	-	-	-	-	-	37.5	-	3	3	107
BF 3	50	-	-	-	-	-	50	-	3	3	94
BF 4	50	-	-	-	-	-	-	25	3	3	119
BF 5	50	-	-	-	-	-	-	50	3	3	94

*All the quantities are weighed in mg

Table 3. Post-compression parameters of Bilayer tablet formulations

Formulation Code	Thickness (n =5) (mm) ±σ	Hardness (n=5) (kg/cm2) ±σ	Weight Variation (n=10) (mg) ±σ	Friability (%)	Content Uniformity (%)
BF 1	5.07 ± 0.02	7.05±0.1	349.8±1.32	0.56±0.02	99.42±0.65
BF 2	5.02±0.00	7.02±0.05	349.9±0.66	0.52±0.87	99.67±0.06
BF 3	5.03 ± 0.05	6.78±0.09	349.8±1.06	0.56±0.67	99.78±0.13
BF 4	5.01±0.02	6.62±0.02	349.8±0.62	0.40±0.04	99.58±0.24
BF 5	5.00±0.02	6.54±0.03	349.1±0.39	0.50±0.03	100.4±0.34

Table 4. *In vitro* release data of Bilayer Mucoadhesive tablets BF 1- BF 5

Time (hr)	BF 1	BF 2	BF 3	BF 4	BF 5
0	0	0	0	0	0
0.25	12.27	10.55	9.79	10.32	9.25
0.5	25.65	20.26	17.15	21.56	17.53
1	31.01	25.78	23.34	27.89	22.61
2	35.17	30.64	26.72	38.67	30.20
3	39.42	34.37	31.23	54.33	37.49
4	43.91	39.05	3411	58.42	43.67
5	47.83	44.66	37.79	-	-
6	54.56	48.83	40.71	-	-
7	60.35	52.12	43.08	-	-
8	63.99	56.09	45.89	-	-
9	67.25	61.52	49.97	-	-
10	71.28	66.75	53.03	-	-
11	75.44	70.96	56.79	-	-
12	-	73.36	61.32	-	-

Table 5. Swelling data of Bilayer Mucoadhesive tablets BF1-BF3

Time (hrs)	BF 1	BF 2	BF 3
2	66.78	71.22	79.66
4	83.45	96.83	115.6
6	108.35	105.36	122.49
8	95.36	119.34	130.75
10	0	130.94	138.99
12	0	141.63	152.52

Table 6. Regression analysis of the *In vitro* release data according to various release kinetic models for BF1- BF5

Formulation code	Zero order	First order	Higuchi	Korsmeyer- Peppas	
	R^2	R^2	R^2	R^2	n
BF 1	0.878	0.976	0.969	0.874	0.399
BF 2	0.943	0.980	0.987	0.973	0.446
BF 3	0.921	0.966	0.985	0.977	0.415
BF 4	0.930	0.971	0.987	0.970	0.594
BF 5	0.910	0.951	0.994	0.973	0.521

Fig 1. FTIR spectra of pure drug Lovastatin

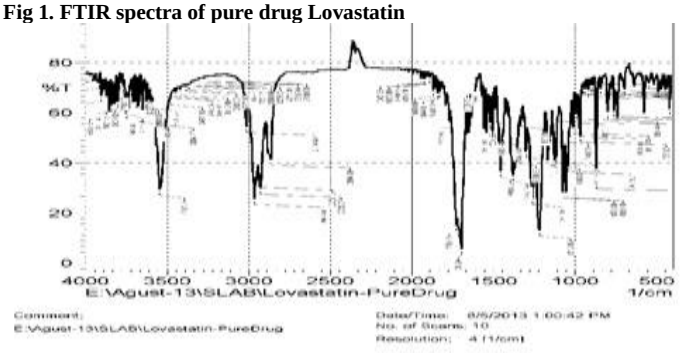


Fig 2. FTIR spectra of Optimised sustained release formulation containing HPMC K 100

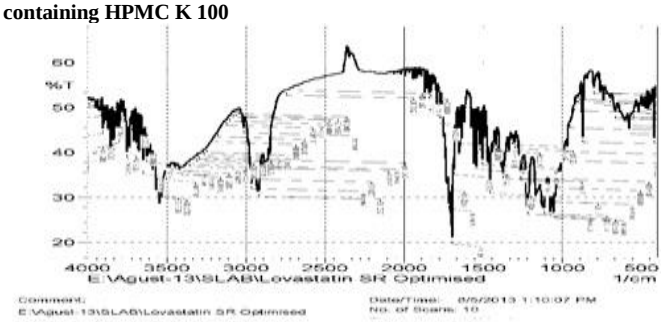


Fig 3. FTIR spectra of Optimised immediate release formulation containing SSG and CP

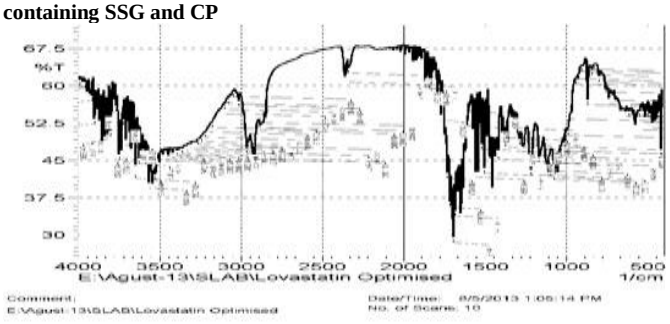


Fig 4. In vitro release data of Bilayer Mucoadhesive tablets BF1- BF5

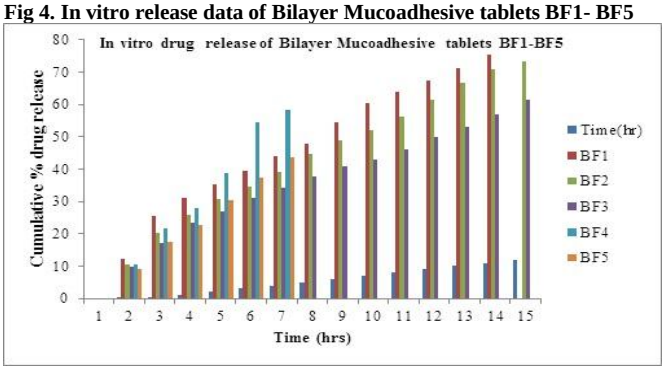


Fig 5. % Swelling index of bilayer mucoadhesive tablets BF1-BF3

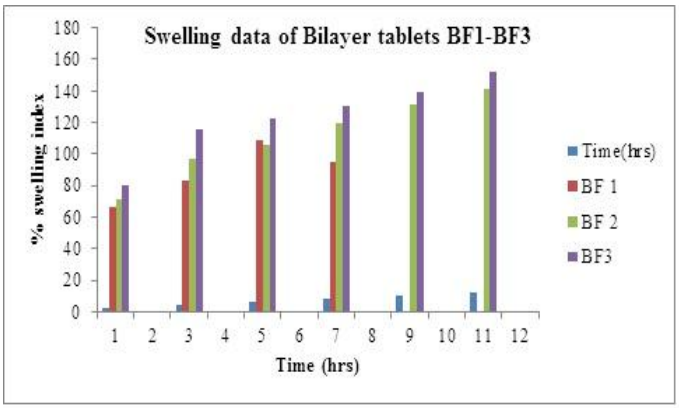


Fig 6. Zero order release plot

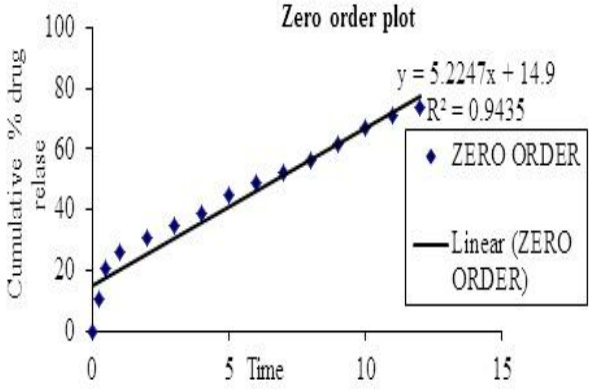


Fig 7. First order release plot

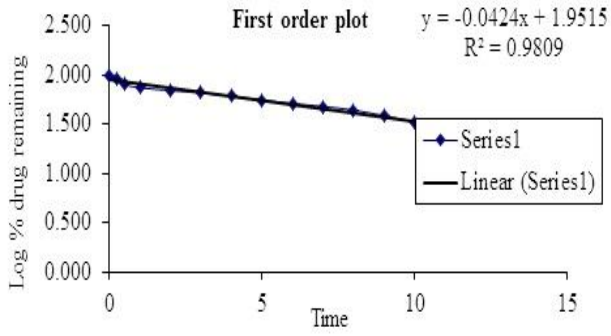


Fig 8. Higuchi plot

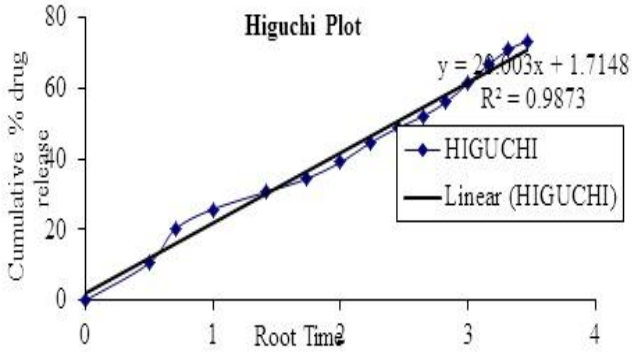
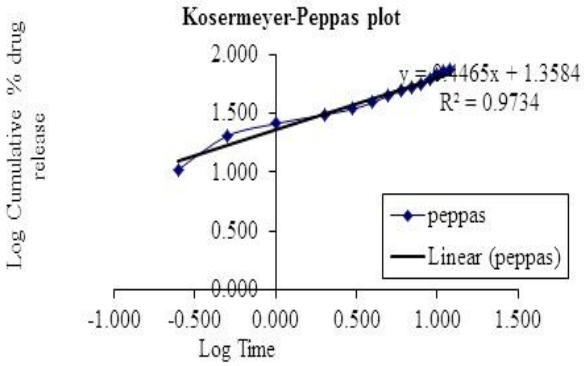


Fig 9. Kosermeyer-Peppas plot



Evaluation of post-compression parameters of Bilayer tablet formulations

Drug release kinetics of Optimised bilayer mucoadhesive BF 2 formulation

Drug release kinetics: To investigate the mechanism of drug release from bilayer mucoadhesive tablets, various kinetic models like zero order, first order, Higuchi, Korsmeyer- Peppas equations were applied to the *In vitro* release data obtained from different formulations. Diffusion exponents (n) were determined for all the formulations (0.135-0.594). From the observations it was concluded that the optimized formulation (BF 2) was best explained by first order (R^2=0.980) and Higuchi (R^2=0.987) first order. The drug release was proportional to the square root of time indicating that the drug release was diffusion controlled. The kinetic release data also suggest the diffusion mechanism to be Fickian diffusion since it indicates a good linearity and as evident from release exponent n=0.446. The results of kinetic study are shown in Table 6.

CONCLUSION

The present study was conducted to develop bilayer mucoadhesive tablets of Lovastatin containing fast release layer and the sustain release layer using different polymers in different concentrations. Optimized

formulation BF 2 showed an excellent mucoadhesion and bimodal drug release pattern. This could be advantageous in terms of increased bioavailability. Bilayer tablets showed an initial burst effect to provide the loading dose of the drug, followed by sustained release for 12 h, indicating a promising potential of Lovastatin bilayer tablet.

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