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FORMULATION AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE TABLETS OF SIMVASTATIN

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Abstract:
The present study focused on the development and optimization of gastroretentive mucoadhesive tablets of Simvastatin using direct compression technique. Preformulation studies confirmed its physicochemical properties, solubility profile, and purity, with λmax observed at 231 nm in 0.1 N HCl and excellent linearity (R^2 = 0.995). FT-IR analysis revealed no drug–excipient interactions, ensuring compatibility. Powder blends demonstrated acceptable flow and compressibility (angle of repose 26–31°, compressibility index 25–35%, Hausner's ratio 1.33–1.55), supporting ease of processing. Post-compression evaluation showed uniform weight, thickness, diameter, hardness (5.0–5.5 kg/cm²), friability (<1%), and drug content (98–99%), confirming mechanical strength and dosage uniformity. The tablets exhibited excellent swelling behavior (97–121% hydration after 12 hr), rapid buoyancy initiation (lag time 25–33 sec), and prolonged gastric retention (20–23 hr). Strong mucoadhesion (3.4–3.8 N) further supported gastric residence. In-vitro release studies demonstrated sustained drug release, with dissolution data fitting both Higuchi and Korsmeyer–Peppas models (R^2 = 0.993). The release exponent (n = 0.558) indicated anomalous transport, involving both diffusion and polymer relaxation. Overall, the optimized formulation (GM-4) achieved prolonged gastric retention, controlled release, and enhanced bioavailability of Simvastatin. This once-daily dosage form offers improved patient compliance, reduced dosing frequency, and better therapeutic outcomes in the management of hypercholesterolemia and cardiovascular disease risk. The study highlights gastroretentive mucoadhesive tablets as a promising approach for sustained oral delivery of Simvastatin

KEYWORDS: *Gastroretentive, Mucoadhesive, Ttablet, Simvastatin, Compression*

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INTRODUCTION:

Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer[1]. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs[2]. The application of mucoadhesive tablets to the mucosal tissues of gastric epithelium is used for administration of drugs for localized action[3]. Mucoadhesive tablets are widely used because they release the drug for prolong period, reduce frequency of drug administration and improve the patient compliance[4]. Interest in controlled and sustained release drug delivery has increased considerably during the past decade and, in selected areas, it's now possible to employ fairly sophisticated system which is capable of excellent drug release control[5].

Simvastatin is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which converts HMG CoA into mevalonate, a precursor in cholesterol synthesis[6]. The poor bioavailability necessitates the development of an efficient delivery system which can improve the oral bioavailability of simvastatin[7]. Poor bioavailability has been recorded for some drugs formulated in sustained-release dosage forms[8]. Their narrow absorption window, lower solubility at high pH values, or enzymatic degradation in the intestinal or colonic environments was the reason of decreased bioavailability[9]. For this, it has been a challenge to develop the oral controlled-release dosage form because it is difficult to keep drugs at the targeted area inside the gastrointestinal tract[10]. Gastro retentive drug delivery systems provide dosage forms with a longer residence time in the stomach and sustained-release behavior, which can improve bioavailability[11]. Increasing gastric residence time can be achieved either by mucoadhetion systems that cause adhesion to gastric wall mucosa, that sink to the wall of the stomach bioadhesive systems that adhere to mucosal surfaces, or by expandable systems that have limited emptying through the stomach pylorus due to swelling or unfolding to a larger size[12].

The objective of this study was to develop and optimize Mucoadhesive tablets of simvastatin to overcome its oral bioavailability (<5%) caused by extensive first-pass metabolism.

MATERIALS AND METHOD:

Simvastatinwas obtained from Synokem Pharmaceuticals, Ltd. Haridwar as gift sample for research purpose. Chitosan, Magnesium stearate were purchased from Qualigens Fine Chemicals, Mumbai, Sodium alginate and Lactose were purchased from S. D. Fine Chem. Ltd., Mumbai. Rest chemicals were belongs to L. R. grade.

Formulation Development of Gastroretentive Mucoadhesive Tablets of Simvastatin

The formulation procedure for gastroretentive mucoadhesive tablets of simvastatin, using a direct compression method for simplicity and efficiency. Simvastatin was mixed with mucoadhesive polymers (chitosan, sodium alginate and polyethylene glycol), CO_2 producing compound Sodium bi carbonate ($NaHCO_3$) and fillers (lactose) in a blender for 20–25 minutes. Lubricants (magnesium stearate and talc) were mixed gently for an additional 5 minutes. The blended powder was compressed using a rotary tablet press fitted with an appropriate punch (8 mm round flat). Target tablet hardness was 5–6 kg/cm².

Pre-compression Evaluation of Blend: There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced, bulk density, true density and percent compressibility index have been measured.

Determination of mucoadhesive strength (*In-vitro* bioadhesion strength): Using a state-of-the-art dynamometer-based microprocessor equipped with a driver's seat (Ultra Test Tensile Strength Tester, Mecmesin, West Sussex, United Kingdom) equipped with a 25 kg weight as described on the sensor, in this test the goat mucous membrane was formed into a circular. It is held firmly on the stainless steel adapter and the gastroretentive mucoadhesive piece to be tested is adhered to another cylindrical stainless wire adapter of similar diameter using a cyanoacrylate bioadhesive. 100 µL of 1% w/v mucin solution is applied to the mucosal surface and the tablets immediately come into contact with the mucosa. At the end of the contact period, the upper support is lifted at a speed of 0.5 mm/s until the tablet is completely removed from the mucosa. Adhesion performance is determined by the area under the force curve. The highest separation force was the maximum force that separates a tablet from the mucosa.

Force of adhesion = (Bioadhesion strength X 9.8)/ 1000

Bond strength = Force of adhesion/ surface area

RESULTS AND DISCUSSION

Preformulation Study: The evaluation performed by sensory characters-taste, appearance, odor, feel

of the drug. It was observed that the simvastatin is a White to off white, odorless, tasteless, solid, crystalline powder. The simvastatin was started melting on 136 ^{O}C and ended the melting on 138 ^{O}C, hence the average melting point 136 ^{O}C – 138 ^{O}C. Solubility of the drug simvastatin was determined at room temperature and found sparingly soluble in distilled water, soluble in 0.1NHCl and phosphate buffer (6.8), Freely soluble in ethanol and methanol and Slightly soluble in 0.1N NaOH. The simvastatin drug was scanned in from 200-400nm and the λmax was observed at 231nm when drug dissolved in 0.1NHCl solution. Calibration curve of Simvastatin was prepared in 0.1 N HCl at λmax 231nm. The linearity equation was founs as Y = 0.010 +0.015 and regreation coefficient (R^2) = 0.995. No significant shift in major peaks of Simvastatin was observed when mixed with excipients. That indicated no chemical interaction, but rather physical inclusion complex formation. In some cases, peak broadening or intensity reduction was observed, which may indicate hydrogen bonding or amorphization. FT-IR confirmed that Simvastatin forms stable physical mixture with polymer and shows no adverse interactions with other polymers. This supports its use in controlled-release formulations.

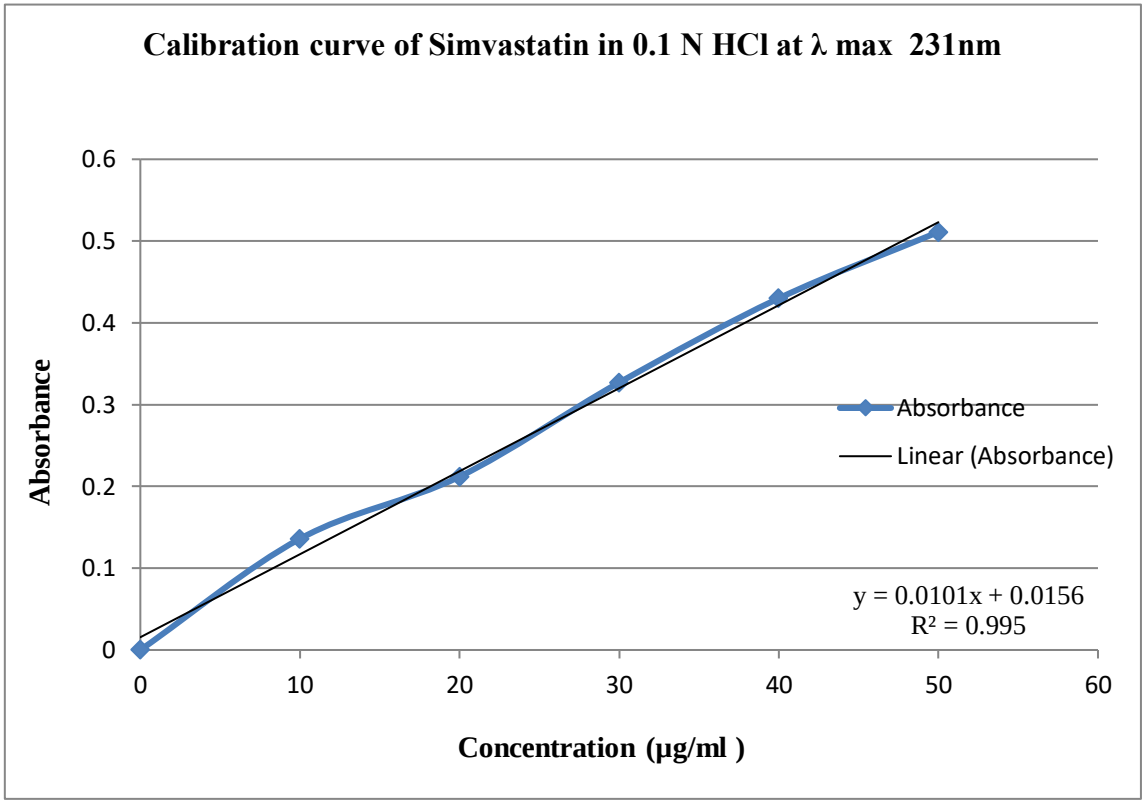

Figure 1: Calibration curve of Simvastatin in 0.1 N HCl at λ max 231nm

Composition of gastroretentive mucoadhesive tablets of simvastatin

Tablet No. 1: Composition of gastroretentive mucoadhesive tablets of simvastatin

Ingredients	Used as	GM-1	GM-2	GM-3	GM-4	GM-5	GM-6
Simvastatin (mg)	API	10	10	10	10	10	10
Chitosan (mg)	MAP	5	6	7	8	9	10
Sodium alginate (mg)	MAP	15	14	13	12	11	10
Lactose (mg)	Filler	50	50	50	50	50	50
PEG (mg)	Plasticizer	5	5	5	5	5	5
Sodium bi carbonate (mg)	CO_2 production	7	7	7	7	7	7
Magnesium stearate (mg)	Lubricant	5	5	5	5	5	5
Talc (mg)	Glident	3	3	3	3	3	3
Total weight	-	100	100	100	100	100	100

API = active pharmaceutical ingradient, MAP = Mucoadhesive polymer

Pre-compression Evaluation of Blend

Angle of repose: The angle of repose of the Simvastatin and polymer blend was determined and found the angle between 26- 31^{O} that indicated medium to good flow ability.

Bulk density and Tapped bulk density: The bulk density and Tapped density of the powders of different formulations were evaluated before the compression of powders in to tablets. The bulk density and the tapped density for all formulations varied from 0.236 to 0.263gm/cm^3 and 0.336 to 0.374gm/cm^3 respectively. Values obtained lies within acceptable range. Difference between the bulk density and tapped density was found very few. This result helps in calculating the % compressibility of powder.

Compressibility index: The results of the Compressibility index of all the formulations ranges from 25.000% to 35.870%. Results of Compressibility index of all the formulations were shown in the Table. Results clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility.

Hausner's ratio: The result of Hausner's ratio of all formulations ranges from 1.333 to 1.559. Results of Hausner's ratio of all formulations were shown in Table which indicates that the flow ability of all the formulation.

Table No. 2: Result of pre-compression properties of Simvastatin powder blend

Code	Angle of Repose (^{O})	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hausner ratio
GM-1	29	0.245	0.365	32.877	1.490
GM-2	30	0.263	0.374	29.679	1.422
GM-3	28	0.252	0.336	25.000	1.333
GM-4	28	0.241	0.372	35.215	1.544
GM-5	31	0.236	0.368	35.870	1.559
GM-6	26	0.248	0.361	31.302	1.456

Post-Compression Evaluation of Simvastatin Gastroretentive Mucoadhesive Tablet:

General appearances: Five tablets from various batches were randomly selected and evaluated. Appearance was judged visually as 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 and standard deviation were calculated. The average value of thickness was calculated in the range of (2.01 ± 0.02) to (2.14 ± 0.03) mm and tablet diameter was measured as (7.94 ± 0.03) to (8.13 ± 0.03) mm, the tablets were prepared within the limited range of standard deviation that indicated the thickness and diameter were uniform. The thickness of the tablets was reported in the millimeter (mm).The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm).

Weight uniformity: Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded and is shown in Table. The obtained data were almost uniform. The values of tablets average weight ranging from (160 ± 1) to (175 ± 3) mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ± 7.5% of the weight.

Hardness: The mean hardness values were measured for all the formulation using Monsanto hardness tester. The results were tabulated below observed the hardness value ranges from 5.0 ± 0.1 to 5.5 ± 0.2 kg/cm^2.

Table No. 3: Post-Compression Evaluation of gastroretentive mucoadhesive tablets

Code	General Appearance	Thickness ± S.D. in mm)	Diameter ± S.D. in (mm)	Weight ± S.D. in (mg)	Hardness ± S.D. (kg/cm^2)	Friability (%) (n =3)	Drug content (%) (n =3)
GM-1	+++	2.05 ± 0.01	8.12 ± 0.02	163 ± 3	5.2 ± 0.1	0.727 ± 0.015	99.25 ± 0.42
GM-2	+++	2.14 ± 0.03	7.94 ± 0.03	160 ± 1	5.2 ± 0.2	0.751 ± 0.012	99.01 ± 0.38
GM-3	++	2.12 ± 0.01	8.01 ± 0.01	175 ± 3	5.5 ± 0.2	0.698 ± 0.009	98.49 ± 0.44
GM-4	+++	2.09 ± 0.03	8.04 ± 0.02	163 ± 1	5.0 ± 0.1	0.722 ± 0.010	98.51 ± 0.16
GM-5	+++	2.01 ± 0.02	8.13 ± 0.03	162 ± 1	5.2 ± 0.2	0.637 ± 0.007	98.38 ± 0.18
GM-6	+	2.13 ± 0.01	8.04 ± 0.03	173 ± 2	5.2 ± 0.1	0.734 ± 0.004	98.32 ± 0.25

Friability: Friability determines the strength of the tablets during transportation. The observed values of friability test were reported in the Table below. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friabilitytest indicate that the tablet possesses good mechanical strength. The friability valueranges from (0.637 ± 0.007) to (0.751 ± 0.012).

Drug content: The % drug content of all the formulated tablets were found within the limit. The % drugcontent value of Simvastatin was within 98.32 ± 0.42 % to 99.25 ± 0.42 %. The results within the range indicated uniformity of mixing.

Swelling index: Percent hydration (swelling index) was calculated and tabulated below. Percent hydration of the gastroretentive mucoadhesive tablets after 12 hour was ranged in (97.47) to (121.27).

Table No. 4: Swelling index of the gastroretentive mucoadhesive tablets

Formulation code	Percent hydration			
	2 hrs.	4 hrs.	8hrs.	12hrs.
GM-1	79.18	97.38	101.53	121.27
GM-2	59.29	68.71	88.29	99.47
GM-3	65.47	85.36	99.78	103.68
GM-4	57.23	76.43	93.32	106.16
GM-5	52.45	69.62	87.61	97.47
GM-6	61.16	75.64	94.42	99.18

***In-vitro* Buoyancy studies:** *In-vitro* Buoyancy studies the gastroretentive mucoadhesive tablets was determined and the Gastroretentive lag time ranged from 25.28 to 32.64 sec. and Total gastroretentive time ranged from 20.31 to 23.26 Hrs.

Table No. 5: *In-vitro* Buoyancy studies the gastroretentive mucoadhesive tablets

S. No.	Formulation Code	Gastroretentive lag time (sec.)	Total gastroretentive time (Hrs.)
1	GM-1	25.28	23.26
2	GM-2	26.38	21.14
3	GM-3	27.25	20.31
4	GM-4	30.28	21.71
5	GM-5	26.42	22.22
6	GM-6	32.64	22.87

Determination of mucoadhesive strength (*In-vitro* bioadhesion strength): Bioadhesion strength of the gastroretentive mucoadhesive tablets was measured it was found in range of 3.4 to 3.8 (N).

Table No. 6: Bioadhesion strength of the gastroretentive mucoadhesive tablets

S. No.	Formulation Code	Bioadhesion strength (N)
1	GM-1	3.5
2	GM-2	3.7
3	GM-3	3.4
4	GM-4	3.8
5	GM-5	3.6
6	GM-6	3.4

***In-vitro* drug release studies:** The *in-vitro* drug release profiles for the preliminary formulations were tabulated below. The plot of cumulative percentage drug release V/s time (Hrs) for preliminary formulations were plotted and depicted in Figure.

Table No. 7: *In-vitro* drug release studies of the gastroretentive mucoadhesive tablets

Time (Hrs)	% Cumulative Drug Release					
	GM-1	GM-2	GM-3	GM-4	GM-5	GM-6
1	12.02	22.60	20.15	25.16	10.11	10.47
2	32.02	34.82	33.56	39.72	30.21	25.23
3	40.43	42.13	39.89	46.48	39.69	35.61
4	51.44	56.04	54.81	58.72	49.61	45.34
6	60.50	69.71	65.14	73.59	56.24	52.56
8	69.54	75.55	73.32	85.41	65.75	69.72
10	76.15	83.77	82.43	92.95	73.17	72.39
12	86.26	91.48	89.79	99.00	83.02	80.53

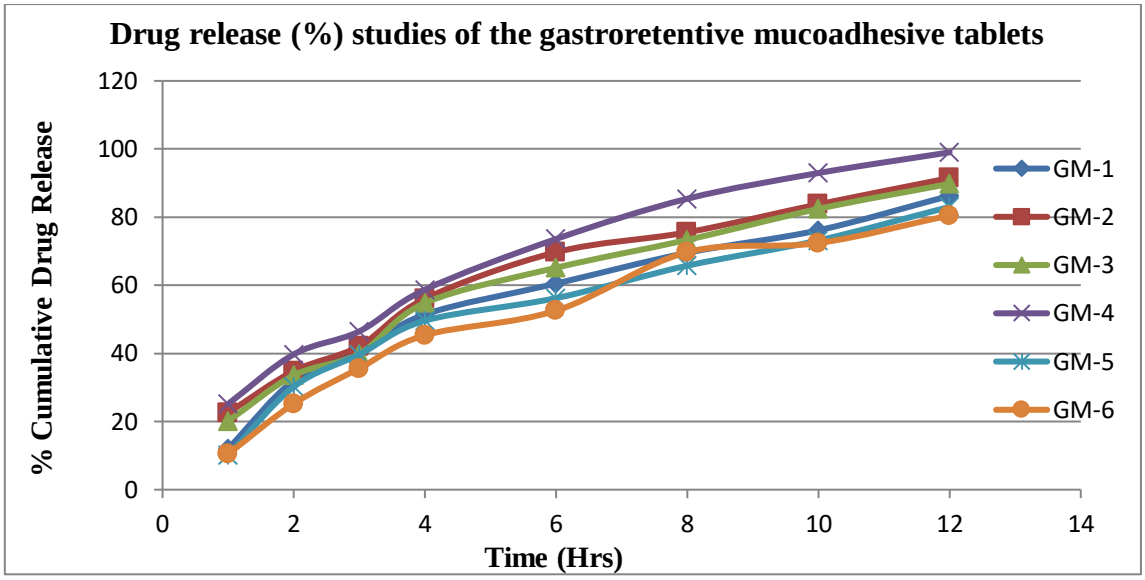

Figure 2: Drug release (%) studies of the gastroretentive mucoadhesive tablets

7.5 Kinetic Modelling of *In-Vitro* Release Data of GM-4

Table No. 8: Kinetic Modelling of *In-Vitro* Release Data of GM-4

Time (Hrs)	Square Root of Time	Log Time	Cumulative % Drug Release	Log Cum % Drug Release	Cumulative % Drug Remaining	Log Cum % Drug Remaining
1	1	0	25.16	1.401	74.84	1.874
2	1.414	0.301	39.72	1.599	60.28	1.780
3	1.733	0.477	46.48	1.667	53.52	1.728
4	2.000	0.602	58.72	1.769	41.28	1.615
6	2.448	0.778	73.59	1.867	26.41	1.422
8	2.827	0.903	85.41	1.932	14.59	1.164
10	3.162	1.000	92.95	1.968	07.05	0.848
12	3.464	1.079	99.00	1.996	01.00	0.000

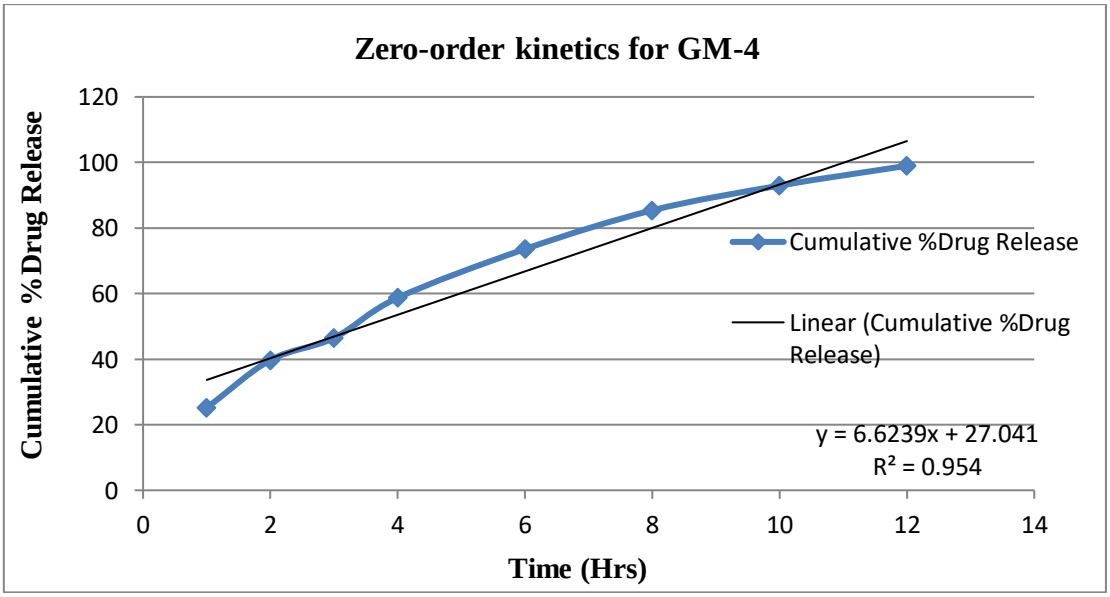

Figure 3: Zero-order kinetics for GM-4

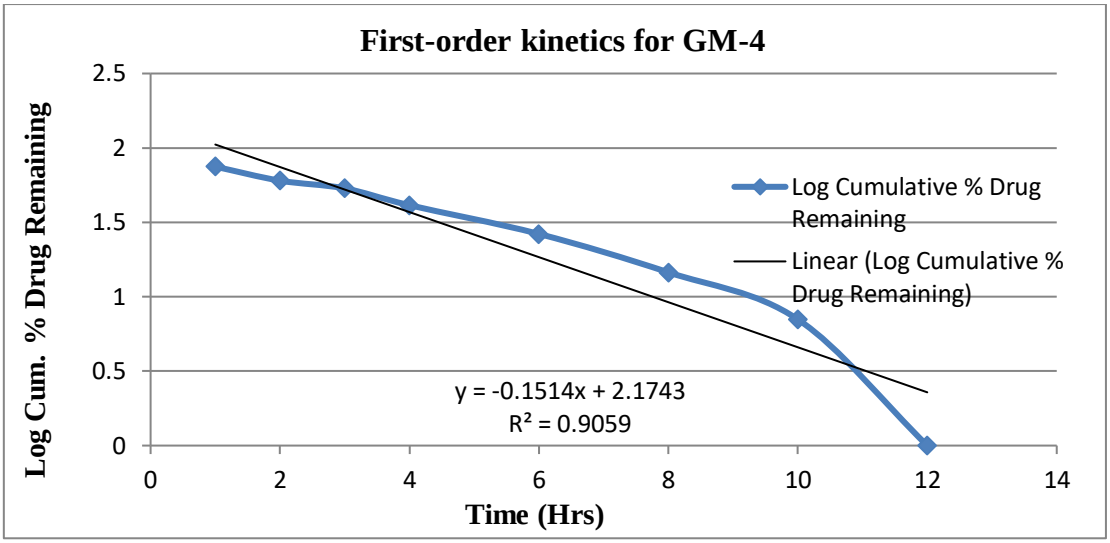

Figure 4: First-order kinetics for GM-4

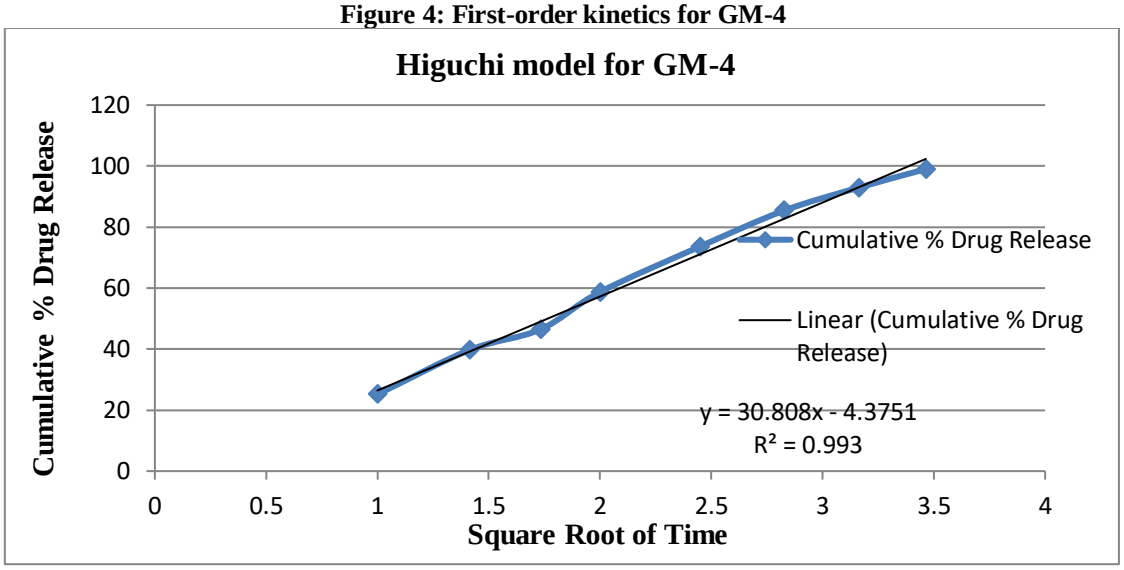

Figure 5: Higuchi model for GM-4

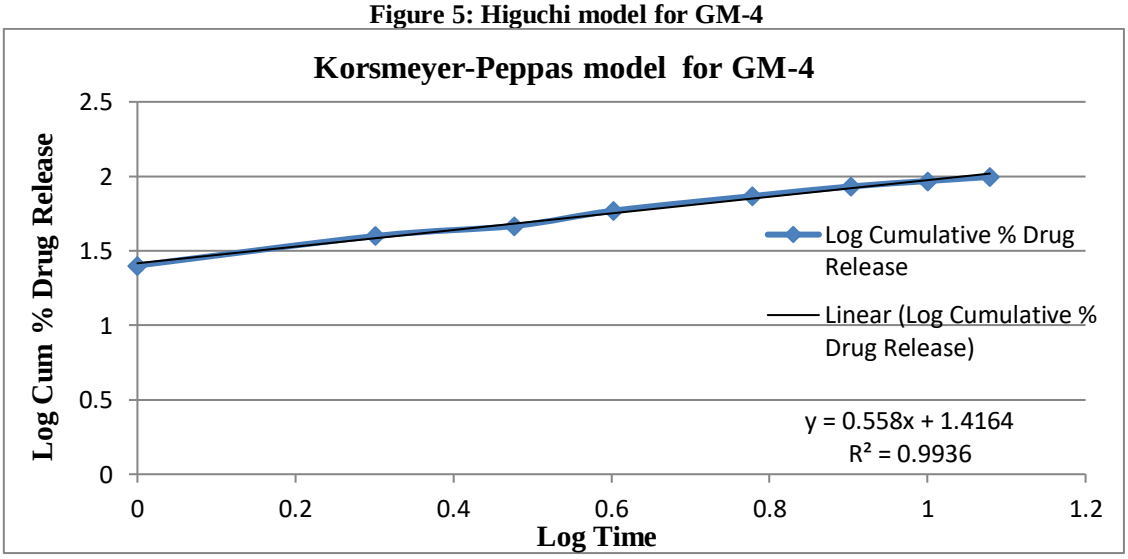

Figure 6: Korsmeyer-Peppas model for GM-4

Table No. 9: Analysis of Kinetic Modelling for GM-4

Name of model	Regression equation	Regression Coefficient (R^2)
Zero-order	y = 6.623x + 27.04	R^2 = 0.954
First-order	y = -0.151x + 2.174	R^2 = 0.905
Higuchi model	y = 30.80x - 4.375	R^2 = 0.993
Korsmeyer-Peppas model	y = 0.558x + 1.416	R^2 = 0.993

The Korsmeyer–Peppas and Higuchi models yield the same high R^2 value (0.993), it suggests that both models fit the drug release data equally well. But the twist was: while the fit is statistically similar, the mechanistic interpretation can still differ. Higuchi assumes Fickian diffusion from a homogeneous matrix. Korsmeyer–Peppas is more flexible, it can describe Fickian, non-Fickian, or Case II transport, depending on the release exponent (n).

The release data matches both models statistically then to understand the mechanism consider the release exponent (n) from Korsmeyer–Peppas. The 'n' value from Korsmeyer–Peppas was greater to 0.5 (i.e. 0.558) it indicated Anomalous (non-Fickian) transport.

CONCLUSION:

The present investigation successfully developed and optimized gastroretentive mucoadhesive tablets of Simvastatin using direct compression technique. The preformulation studies confirmed the physicochemical characteristics and solubility profile of Simvastatin, highlighting its suitability for a gastric retention system. The drug demonstrated a distinct λ_{max} at 231 nm in 0.1 N HCl**,** with excellent linearity (R^2 = 0.995), supporting its quantitative analysis. FT-IR spectroscopy revealed no significant chemical interactions between Simvastatin and polymers, indicating compatibility and stable formulation. The prepared powder blends showed acceptable flow properties (angle of repose, compressibility index, and Hausner's ratio), ensuring good processability. Post-compression parameters such as weight variation, hardness, friability, drug content, swelling index, buoyancy, bioadhesion strength**,** and *in-vitro* drug release were all within pharmacopoeial limits. The formulation exhibited prolonged gastric retention (up to 23.26 hours), excellent swelling behavior, and strong mucoadhesion**,** enhancing Simvastatin's bioavailability. Drug release kinetics matched both Higuchi and Korsmeyer–Peppas models with R^2 = 0.993; however, an exponent value n = 0.558 indicated an anomalous (non-Fickian) transport mechanism, combining both diffusion and polymer relaxation.

On the basis of evaluation parameters, the optimized formulation GM-4 may be used once a day administration in the management of hypercholesterolemia and to reduce the risk of cardiovascular disease. This may improve the patient compliance by reducing the dosing frequency for cardiovascular disease (hypercholesterolemia). Which will ultimately improve the therapeutic outcome? We could be able to minimize the per oral cost of the formulation.

Thus, the formulated gastroretentive mucoadhesive tablets of Simvastatin offer a promising approach for sustained drug release and improved therapeutic efficacy.

CONFLICT OF INTERESTS

There are no any conflicts of interest.

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