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FORMULATION AND EVALUATION OF SIMVASTATIN MATRIX TABLETS

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Abstract:
The Purpose of this Research work was to Formulate and Evaluate Anti-Hyperlipidemic Drug (HMG-coA reductase Inhibitor) in a Controlled discharge dose type of Simvastatin Matrix Tablets.The Tablets were Prepared by utilizing HMPC K15M, HMPC K100M, MicroCrystalline Cellulose , sodium CMC, Magnesium Streate and concentrated with various rate Controlling polymers. The Technique Employed is the Preparation of Matrix Tablet framework by direct Compression Matrix.The Sustainability of the medication is safe,Effective and stable Controlled Release Dosage type of HMPC K100M at centralization of 40mg in blend with Ethyl Cellulose at20mg was seen as acceptable Sustainability and 99% medication discharge in 24 hrs. The enhanced Formulation was assessed with Parameters like Thickness, friability , weight Variation, medicate Content, Invitro Drug discharge and Results were seen as inside the Limits.

Keywords: *Matrix tablets, HMPC K15M, HMPC K100M, MicroCrystalline Cellulose, Controlled discharge, Simvastatin*

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INTRODUCTION:

Atherosclerosis is a general term describing any hardening (loss of elasticity) of the medium of large arteries (in Greek, "Arterio" meaning artery and "sclerosis" meaning hardening), is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens, and eventually blocks the arteries [1]. Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of Aspergillus terreus. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Also, it has been reported [2, 3] that simvastatin is more efficiently extracted by the liver than its corresponding hydroxy acid with subsequent minimization of systemic burden [4]. This suggests that compared to a conventional dosage form, a sustained/controlled release dosage form of simvastatin might provide similar or better efficacy [5]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive drug delivery system (GRRDS). GRRDS extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals but also increase patient compliance beyond the level of existing controlled release dosage form [6]. A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts such as Floating Systems [7], Bio/Mucoadhesive Systems [8], and Swelling and expanding systems [9], High-Density Systems [10], Incorporation of passage delaying food agents [11], Ion exchange resins [12], and Osmotic regulated systems [13].

Atherosclerosis is a general term describing any hardening (loss of elasticity) of the medium of large arteries (in Greek, Arterio" meaning artery and "sclerosis" meaning hardening), is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens, and eventually blocks the arteries [1]. Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of Aspergillus terreus. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Also, it has been reported [2, 3] that simvastatin is more efficiently extracted by the liver than its corresponding hydroxy acid with subsequent minimization of systemic burden [4]. This suggests that compared to a conventional dosage form, a sustained/controlled release dosage form of simvastatin might provide similar or better efficacy [5]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive drug delivery system (GRRDS). GRRDS extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals but also increase patient compliance beyond the level of existing controlled release dosage form [6]. A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts such as Floating Systems [7], Bio/Mucoadhesive Systems [8], and Swelling and expanding systems [9], High-Density Systems [10], Incorporation of passage delaying food agents [11], Ion exchange resins [12], and Osmotic regulated systems [13].

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, accurate dosage and easy production, solid oral dosage forms have many advantages over other types of oral dosage forms [1,2] . Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration [3] . In fact, most new chemical entities's are poorly water soluble

drugs, not well-absorbed after oral administration [4] , which can detract from the drug's inherent efficacy [5-7]. Moreover, most promising new chemical entities's, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, that there is a small absorption window [8,9]. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [10,11]. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [12-14]. Solubility is an important physicochemical factor affecting the absorption of drugs and their therapeutic effectiveness. Poor aqueous solubility leads to formulation development failures. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability and an increase in dosage and variability in blood concentrations [15]

The present task is proposed to detail controlled delivery tablets as framework form. Different rate controlling polymers are utilized to shape a lattice.

The cholesterol union is demonstrated to me more in the mid night, as the simvastin half-life is lessits dosing recurrence ought to be expanded, subsequently to maintain a strategic distance from this a controlled delivery framework definition is proposed.

MATERIALS:

Simvastatin Purchased from Pharmatech solutions, Hyderabad. HPMC K15M, HPMC K100M, Microcrystaline cellulose, Aerosil, Sodium CMC from Pharmatech solutions, Hyderabad.

METHODOLOGY:

Formulation of simvastatin matrix tablets:

The matrix tablets were prepared by following the General Methodology as given below:

The procedure followed was direct compression

The drug and all the excipients except magnesium stearate and aerosil were weighed appropriately and were passed through sieve no.30

Magnesium stearate and aerosil were passed through mesh no.60

All the ingredients were mixed thoroughly in a polythene bag and compressed to a tablet

Table 1: Formulation table For design of Controlled release tablets of Simvastatin:

Formulation code/Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Simvastatin	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K 4M	10	20	30	40	-	-	-	-	-	-	-	-
HPMC K 15 M	-	-	-	-	10	20	30	40	-	-	-	-
HPMCK 100 M	-	-	-	-	-	-	-	-	10	20	30	40
Ethyl cellulose	20	20	20	20	20	20	20	20	20	20	20	20
PVP K 30	5	5	5	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	72.6	62.6	52.6	42.6	72.6	62.6	52.6	42.6	72.6	62.6	52.6	42.6
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Total	150	150	150	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION:

In- vitro dissolution studies of simvastatin controlled released tablets:

The same equipment as in apparatus I was used , expected that a paddle replaced the basket, formed from a blade and a shaft as a stirring element. The dosage form was allowed to sink to the bottom of the flask before stirring . A constant temperature of 37±0.5 ºC was maintained. The motor was adjusted to turn at the specified speed of

50rpm, and the samples of the fluid were withdrawn at intervals to determine the amount of drug in solution.

Dissolution of simvastatin controlleded release tablets:
The dissolution test was carried out using USP apparatus II.
Stirring speed was maintained at 50rpm.
6.8 pH phosphate buffer was used as dissolution medium(900ml) and was maintained at 37±0.5 c
Samples of specified volume were withdrawn at predetermined time intervals, filtered, dilute suitably and assayed spectrophotometrically.
An equal volume of fresh medium was immediately replaced to maintain the dissolution volume.
The sample were analyzed spectrophotometrically at 247.6 nm. Using spectrophotometer to assay the amount of Simvastatinreleased at each time interval.

Table 2: Preformulation studies

Formulation code/Parameter	Bulk density	Tapped density	Angle of repose	Compressibility index	Hausners ratio
F1	0.42	0.53	23.24	26.19	1.26
F2	0.46	0.57	22.26	23.91	1.23
F3	0.44	0.53	23.62	20.45	1.20
F4	0.48	0.56	25.24	16.66	1.16
F5	0.52	0.63	24.69	21.15	1.21
F6	0.51	0.62	23.26	21.56	1.21
F7	0.43	0.54	25.19	25.28	1.25
F8	0.49	0.58	26.92	18.36	1.18
F9	0.55	0.64	23.71	16.36	1.16
F10	0.45	0.55	24.89	22.22	1.22
F11	0.49	0.60	25.59	22.44	1.22
F12	0.50	0.61	23.34	22.00	1.22

Table 3: Post formulation studies

Formulation code/Parameter	Hardness	Weight variation	Friability	Content uniformity
F1	3.0	Pass	0.18	99.17
F2	3.0	Pass	0.22	99.44
F3	3.1	Pass	0.43	98.64
F4	3.0	Pass	0.20	100.2
F5	3.2	Pass	0.38	99.89
F6	3.0	Pass	0.12	99.97
F7	3.0	Pass	0.54	99.25
F8	3.1	Pass	0.19	99.65
F9	3.0	Pass	0.18	99.26
F10	3.2	Pass	0.24	99.48
F11	3.0	Pass	0.27	98.92
F12	3.0	Pass	0.36	99.81

DISCUSSION:

Weight variation : All prepared matrix tablets of Simvastatin were evaluate for weight variation. The weights of all the tablets was found to be uniform with low values of standard deviation and with in the prescribed IP limits.
Hardness and Friability: The hardness of the tablet formulation was found to be in the range of 3 – 3.03 kg/cm^2. The friability values were found to be in the range of 0.10-0.19%.
Drug content: All prepared matrix tablets of Simvastatin were evaluate for uniform drug content. The percent drug content of all the tablets was found to be 98.3-100.02 with low values of standard deviation and with in the prescribed IP limits.

Standard calibration curve of simvastatin:
The standard calibration curve of Simvastatin was developed in different pH media such as 0.1N HCl and pH 7.4 phosphate buffer. Three buffers were selected in order to mimic the in-vivo conditions of the GIT.
Standard Calibration Curve of Simvastatin in 0.1N HCl:

Standard graph of Simvastatin in 0.1N HCl showed linearity in the concentration range of 2-12µg with correlation coefficient of 0.996. Table 6.4 gives the data of the standard graph and Fig 6.1 shows the standard graph in 0.1N HCl.

Table No 4: Calibration curve of 0.1N Hcl

Concentration (µg/ml)	Absorbance
0	0
2	0.149
4	0.265
6	0.387
8	0.473
10	0.593
12	0.708

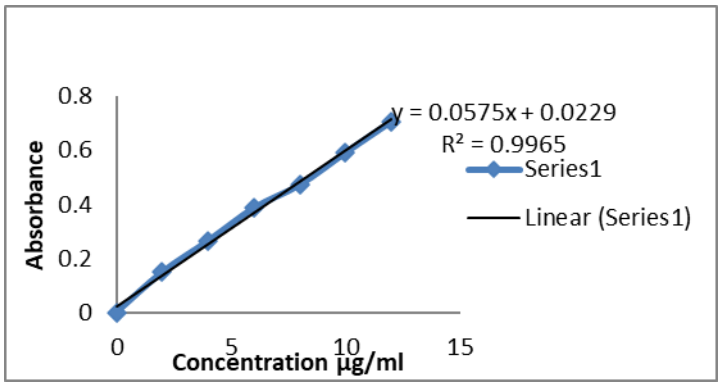


Fig no: 1 Standard Calibration Curve of in 0.1N HCl

Standard Calibration Curve of Simvastatin **in 7.4 pH Phosphate buffer:**

Standard graph of Simvastatin in pH 7.4 phosphate buffer showed linearity in the concentration range of 10-50 µg with correlation coefficient of 0.999. shows the standard graph in pH 7.4 phosphate buffer

Table No 5: Calibration curve of 7.4 pH phosphate buffer

S.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.072
3	20	0.151
4	30	0.221
5	40	0.294
6	50	0.38

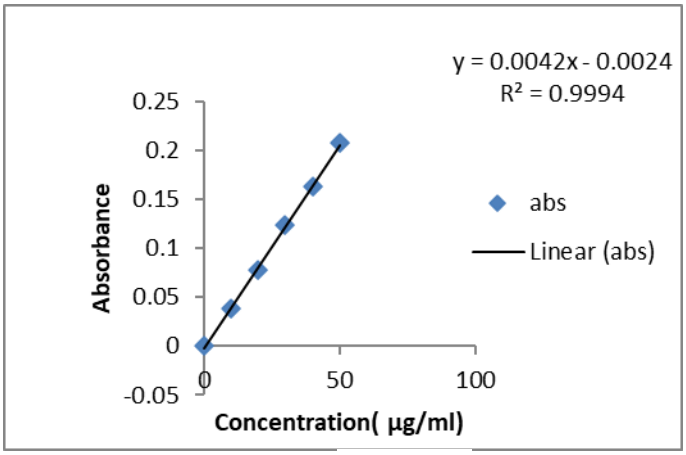


Fig. 2: Standard Calibration Curve of Simvastatin in 7.4 pH Phosphate buffer

Fourier transform infrared spectroscopy (ft-ir) studies:

Drug excipients compatibility study:

To think about the comparability of drug with various polymers, IR Spectra of prescription, polymer and the physical mix of medicine and polymers were taken. The IR Spectra of the prescription and polymer mixes were differentiated and the spectra of unadulterated drug and physical mix of medicine and polymer. The results were acceptable with their brand name ingestion gatherings, the rule tops gained for the blends resembled that of the unadulterated medicine.

The IR Spectra of medicine sodium alginate didn't show a great deal of changes. The possibility of association was blocked as there was no critical move in absorption gatherings of the drug and physical mix, shows that there is no appearance or evaporating of zeniths. It is thusly, foreseen the drug and polymer are great and freed from blend correspondences.

Fig. 3 FT-IR spectra of Simvastatin

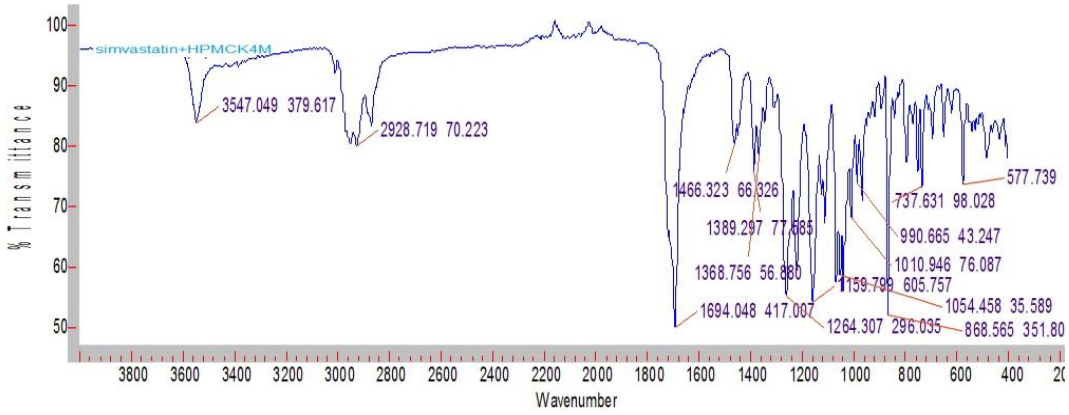


Fig 4 FT-IR spectra of Optimized formulation

Table No 6: Characteristics I.R. Peaks of Drug, Polymers and their Physical Mixtures

S. No.	Drug and Polymers	Characteristic Peaks (cm^{-1})
1.	Simvastatin	3460.68 cm^{-1}, 3021.53 cm^{-1},1466.55 cm^{-1}
2.	Physical mixture of optimized formula	3460.56 cm^{-1}, 3150.22 cm^{-1}, 1466.11 cm^{-1}

DISCUSSION:

3460.68 cm−1, 3021.53 cm−1, and 1466.55 cm−1 identifying with the closeness of handy social events, for instance, Tri-methyl gathering, helper amine get-together, and phenol gathering. The FTIR of Simvastatin and Sodium alginate plan has exhibited outstanding gatherings at 3473.80 cm−1, 3022.45 cm−1, and 1438.90 cm−1 which shows no change in the down to earth social occasions, for instance, Tri-methyl gathering, helper amine get-together, and phenol assembling and attested undisturbed structure of Simvastatin, which shows no medicine excipient joint effort. Propelled specifying has shown outstanding gatherings at 3460.56 cm−1, 3150.22 cm−1, and 1466.11 cm−1 which show no modification in the functional social affairs, for instance, Tri-methyl gathering, helper amine get-together, and phenol assembling and avowed undisturbed structure of Simvastatin. So it shows no drug association in smoothed out arrangement.

Table 7: Invitro dissolution studies

Formulation code/Parameter	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)	F10(%)	F11(%)	F12(%)
1 hr	46	44	34	32	45	43	33	30	44	32	27	19
2 hr	58	56	46	37	58	57	45	42	58	45	35	26
4 hr	69	63	53	49	66	69	54	53	63	55	47	39
6 hr	74	68	68	57	78	75	67	64	67	64	54	48
8 hr	85	78	72	65	92	84	73	68	76	73	63	56
10 hr	98	86	84	73	98	93	86	83	88	85	75	62
12 hr		98	88	87		98	91	88	92	89	84	69
14 hr			96	93			96	91	98	92	89	74
16 hr				98			98	94		98	91	83
18 hr								97			95	88
20 hr											98	91
22 hr												96
24 hr												99

Fig 5: Invitro drug release Plot

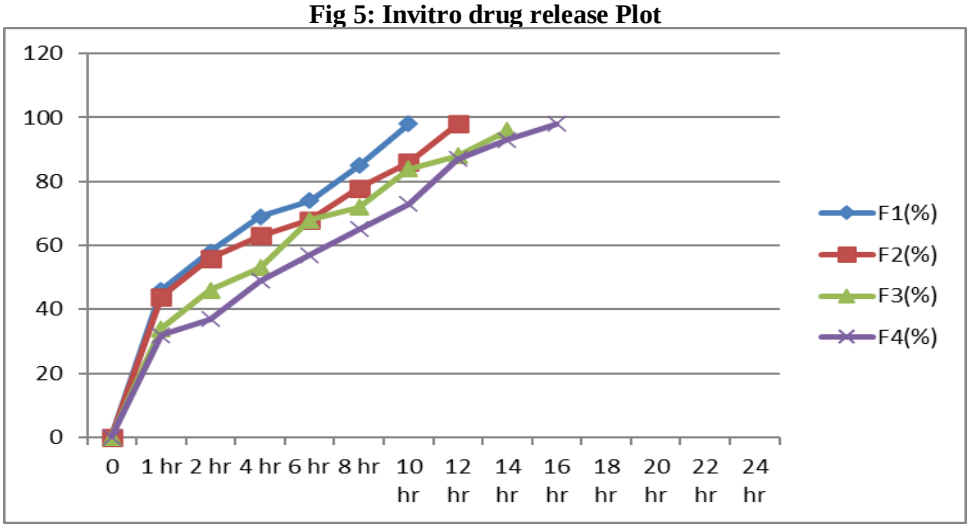


Fig 6: Dissolution graphs with HPMC K 4M

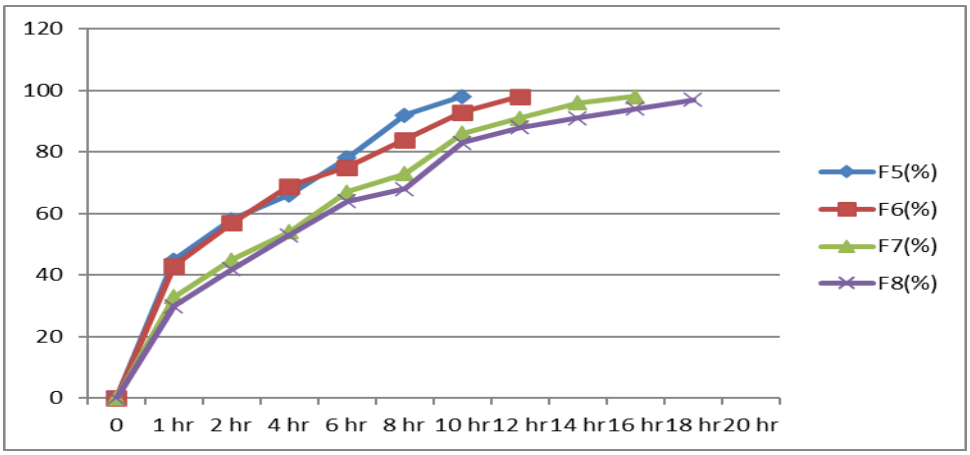
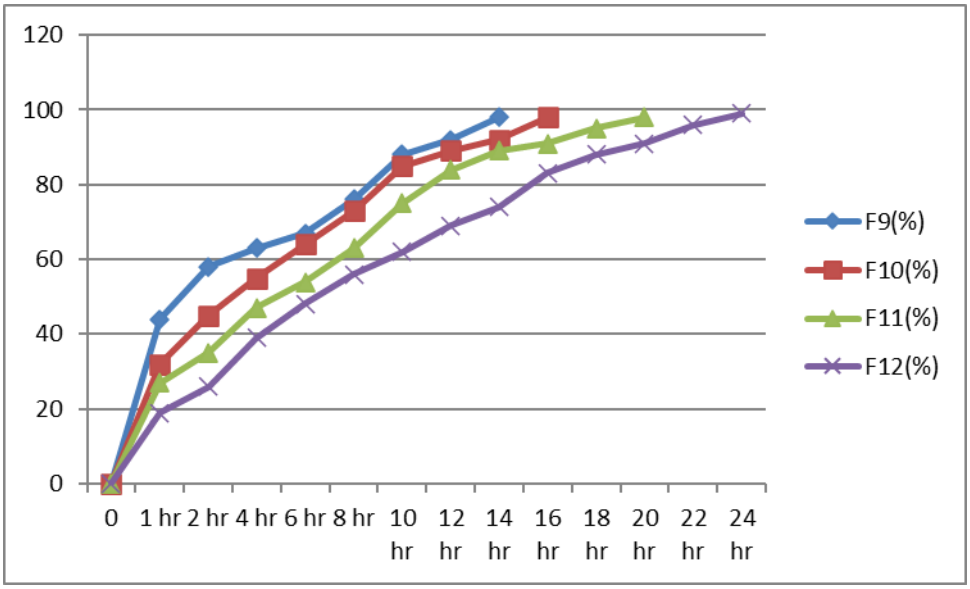


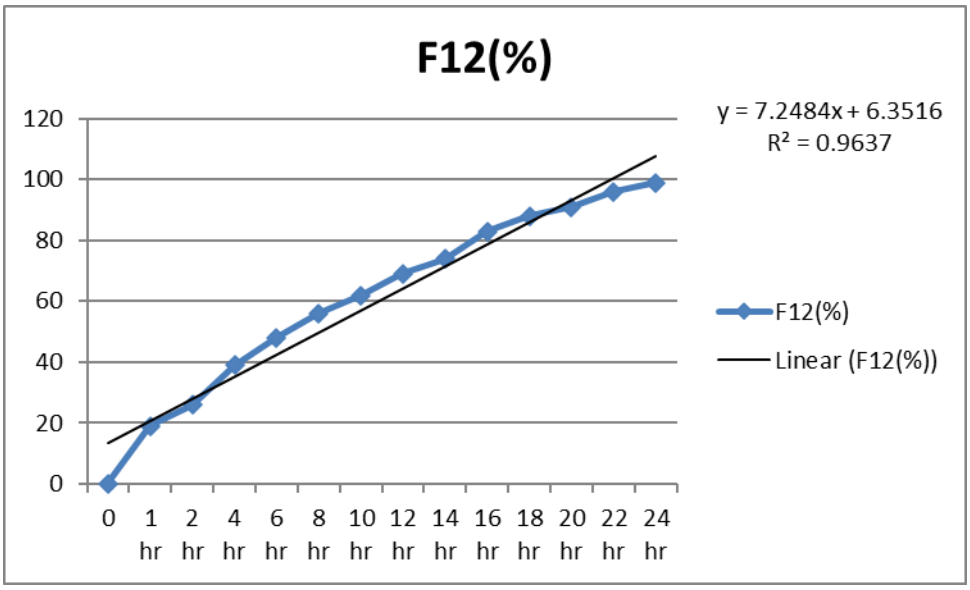
Fig 7: Dissolution graphs for HPMC K 15 M



Release Kinetics for the Best formulation:

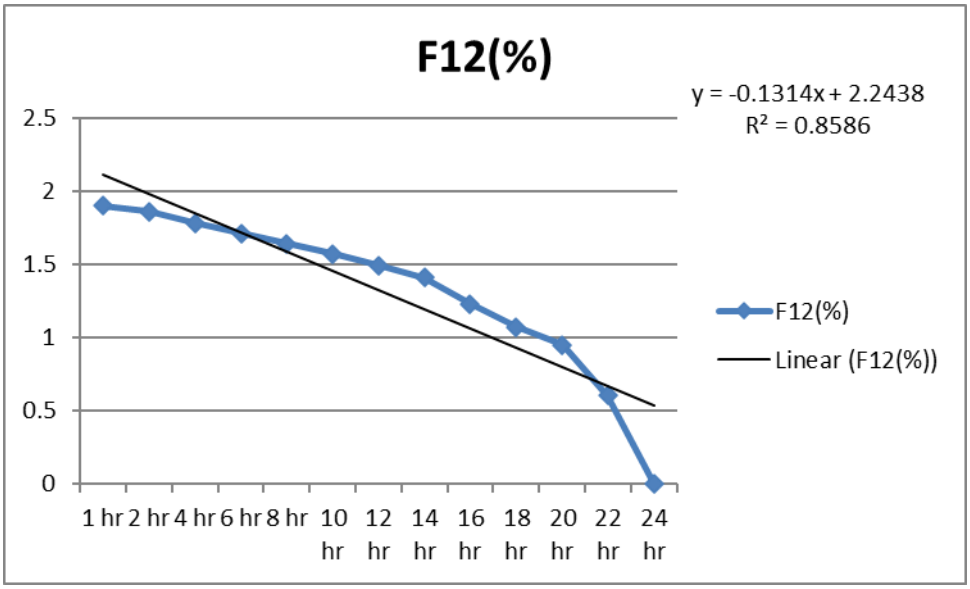
The zero order plot for the best formulation was plotted and is shown in fig no
The regression value was found to be : 0.963

Fig 8: zero order plot



The First order plot for the best formulation was plotted and is shown in fig no The regression value was found to be : 0.858

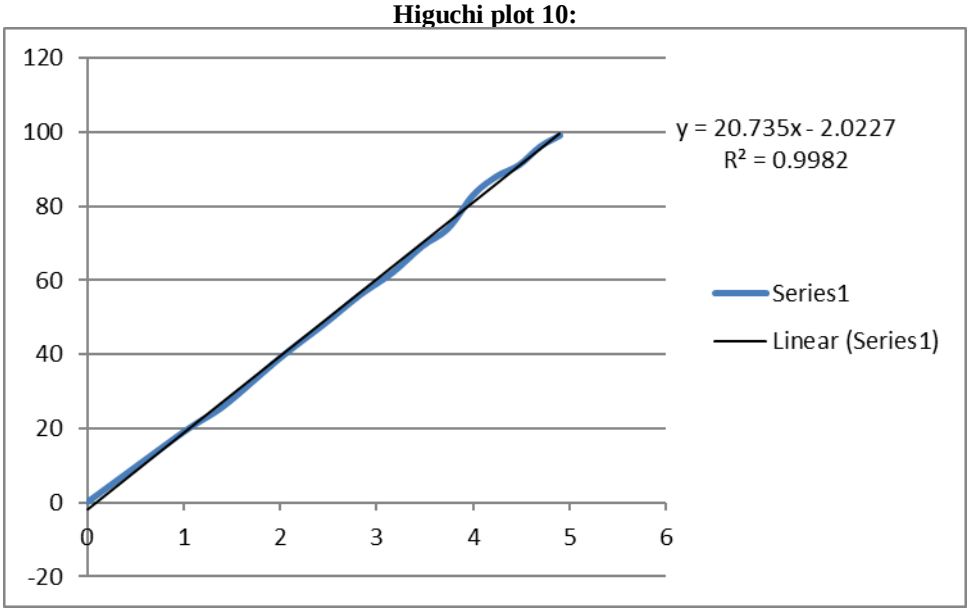
Fig 9: First order Plot for Best formulation



Higuchi plot for Best formulation:

The Higuchi order plot for the best formulation was plotted and is shown in fig no The regression value was found to be : 0.998

Higuchi plot 10:



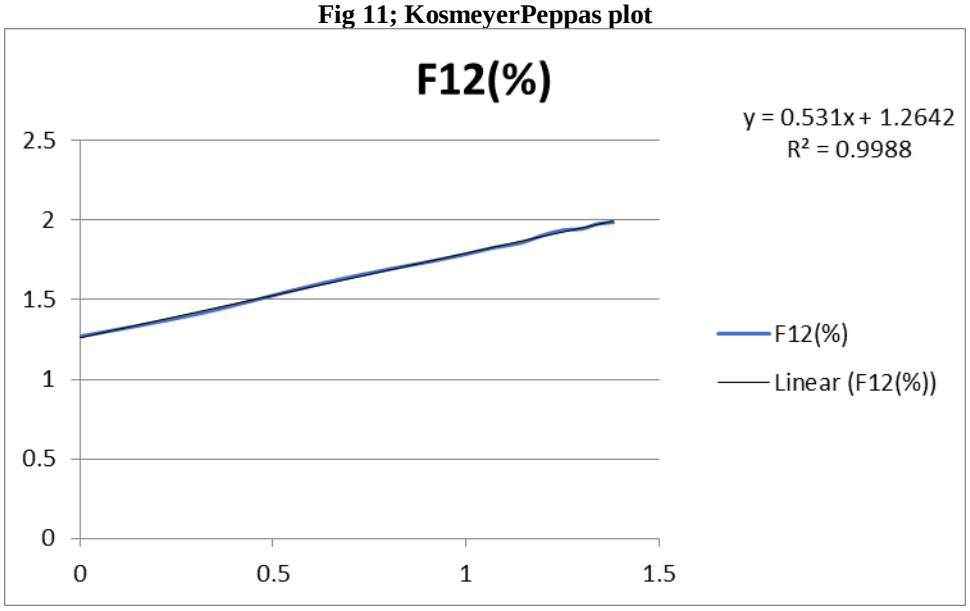
KosmeyerPeppas plot For Best formulation:

The Kosmeyer Pappas plot for the best formulation was plotted and is shown in fig no:

The regression value was found to be :0.998

The n^2 value was found to be : 0.531

Fig 11; KosmeyerPeppas plot



SUMMAY AND CONCLUSION:

Simvastatin is an Antihyperlipidemic tranquilize should be formed into controlled delivery dose structure, for keeping up remedial degrees of powerful treatment and in this way improves tolerant compliance..The approach of the current investigation was to make a near assessment among grouping of these polymers and to evaluate the impact of physico-concoction nature of the dynamic fixings on the medication discharge profile.

The edge of rest, compressibility record and strainer investigation results indicated that the definition is appropriate for Direct pressure.

This investigation have been demonstrated that Simvastatin could be utilized in Controlled delivery medicate conveyance framework by figuring it has supported medication conveyance framework, gives broaden length of activity in helpful range without arriving at harmful levels as on account of regular dose structures. These dose structures can decrease the dosing recurrence and expanding.

The strategy utilized in the arrangement of framework for example Direct pressure, is exceptionally down to earth and practical from the business perspective.

The supportability of the medication with HPMC K 100 M at a grouping of 40 mg in mix with Ethyl cellulose at 20 mg was found to show great maintainability when contrasted with the advertised plan , as it indicated 99% medication discharge for 24 hrs.

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