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Formulation Development and Characterization of Simvastatin Nanoparticles

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ABSTRACT

Simvastatin Is A Lipid-Lowering Medication Drug Which Has Poor Bioavailability Due To Its Insolubility In Water And Belongs To Biopharmaceutics Classification-Ii. The Aim Of This Study Is To Enhance The Bioavailability Of Simvastatin By The Preparation Of Nanoparticles Using Emulsification Solvent Evaporation Method. In Present Work Different Formulations Were Prepared By Using Different Ratios Of Polymer, Span 60. Prepared Nanoparticle Was Evaluated For Its Particle Size, Zeta Potential, Scanning Electron Microscopy, Percentage Practical Yield, Drug Entrapment Efficiency, And In-Vitro Drug Release Studies. Among All The Formulations Dissolution Studies Showed That F3 Formulation Containing 5% Ethyl Cellulose And Eudragit 1:3% As Controlled Release Property And Releases 99.82% At 12h Of Drug In Intestinal Ph (6.8). The Prepared Nanoparticles Forms A Polymer Matrix There By Releases The Drug In A Controlled Manner.

Keywords: Nanoparticles, Ethyl Cellulose, Eudragit and Simvastatin.

INTRODUCTION

The Goal Of Any Drug Delivery System Is To Provide A Therapeutic Amount Of Drug To The Proper Site In The Body To Achieve Promptly And Then To Maintain The Desired Drug Concentration. That Is, The Drug Delivery System Should Deliver Drug At A Rate Dictated By The Needs of The Body Over A Specified Period Of Treatment. This Idealized Objective Points to the Two Aspects Most Important To Drug Delivery Namely Spatial Placement And Temporal Delivery Of A Drug. Spatial Placement Relates To Targeting Of Drug To A Specific Organ Or Tissue, While Temporal Delivery Refers To Controlling The Rate Of Drug Delivery To The Target Tissue. An Appropriately Designed Controlled Release Drug-Delivery System Can Be A Major Advance Towards Solving These Two Problems. It Is For This Reason That The Science And Technology Responsible For Development Of Controlled-Release Pharmaceuticals Has Been, And Continues To Be The Focus Of A Great Deal Of Attention In Both Industrial And Academic Laboratories.

Conventional Drug Therapy[1]

To Gain Appreciation For The Value Of Controlled Drug Therapy, It Is Useful To Review Some Fundamental Aspects Of Conventional Drug Delivery. Consider Single Dosing Of A Hypothetical Drug That Follows A Simple One-Compartment Pharmacokinetic Model For Disposition. Depending On The Route Of Administration, A Conventional Dosage Form Of The Drug E.G.: A Solution, Suspension, Capsule Tablet Etc. Can Produce A Drug Blood Level Versus Time Profile. The Term Drug Blood Levels Refer To The Concentration Of Drug In Blood Or Plasma, But The Concentration In Any Tissue Could Be Plotted On The Ordinate. Administration Of A Drug By Either Intravenous Injection Or An Extra Vascular Route, E.G.,

Orally, Intramuscularly Or Rectally Does Not Maintain Drug Blood Levels Within The Therapeutic Range For Extended Periods Of Time. The Short-Duration Of Action Is Due To The Inability Of Conventional Dosage Forms To Control Temporal Delivery. If An Attempt Is Made To Maintain Drug Blood Levels In The Therapeutic Range For Longer Periods By For E.G., Increasing The Initial Dose Of An Intravenous Injection, Toxic Levels Can Be Produced At Early Times. This Approach Obviously Is Undesirable And Unsuitable. An Alternative Approach Is To Administer The Drug Repetitively Using A Constant Dosing Interval, As In Multiple-Dose Therapy. In This Case The Drug Blood Level Reached And The Time Required To Reach That Level Depend On The Dose And The Dosing Interval. There Are Several Potential Problems Inherent In Multiple Dose Therapy.

1. If The Dosing Interval Is Appropriate For The Biological Half-Life Of The Drug, Large Peaks And Valleys In The Drug Blood Level May Result. For E.G., Drugs With Short Half-Lives Require Frequent Designs To Maintain Constant Therapeutic Levels.
2. The Drug Blood Level May Not Be Within The Therapeutic Range At Sufficiently Early Times, An Important Consideration For Certain Disease States.
3. Patient Non-Compliance With The Multiple-Dosing Regimens Can Result In Failure Of This Approach.

In Many Instances, Potential Problems Associated With Conventional Drug Therapy Can Be Overcome. When This Is The Case, Drugs Given In Conventional Dosage Forms By Multiple Dosing Can Produce The Desired Drug Blood Level For Extended Period Of Time. Frequently, However These Problems Are Significant Enough To Make Drug Therapy With Conventional Dosage Forms Less Desirable Than Controlled-Release Drug Therapy. This Fact, Coupled With The Intrinsic Inability Of Conventional Dosage Forms To Achieve Spatial Placement, Is A Compelling Motive For Investigation Of Controlled-Release Drug Delivery Systems.

Terminology[2, 3]

Modified-Release Delivery Systems May Be Divided Conveniently Into Four Categories:

1. Delayed Release
2. Sustained Release
3. Site-Specific Targeting
4. Receptor Targeting

Delayed-Release Systems Are Those That Use Repetitive, Intermittent Dosing Of A Drug From One Or More Immediate-Release Units Incorporated Into A Single Dosage Form. Examples Of Delayed Release Systems Include Repeat-Action Tablets And Capsules And Enteric-Coated Tablets Where Timed Release Is Achieved By A Barrier Coating.

Sustained-Release Systems Include Any Drug Delivery System That Achieves Slow Release Of Drug Over An Extended Period Of Time. If The Systems Can Provide Some Control, Whether This Is Of A Temporal Or Spatial Nature, Or Both, Of Drug Release In The Body, Or In Other Words, The Systems Is Successful At Maintaining Constant Drug Levels In Target Tissue Or Cells, It Is Considered Controlled-Release Systems.

Site-Specific And Receptor Targeting Refer To Targeting Of A Drug Directly To A Certain Biological Location. In The Case Of Site-Specific Release, The Target Is Adjacent To Or In The Diseased Organ Or Tissues, For Receptor Release, The Target Are The Particular Receptor For A Drug Within An Organ Or Tissue. Both Of These Systems Satisfy The Spatial Aspect Of Drug Delivery And Are Also Considered To Be Controlled Drug-Delivery Systems.

Advantages of Controlled Release Preparations

1. Decreased Incidence And/ Or Intensity of Adverse Effects And Toxicity.
2. Better Drug Utilization.
3. Controlled Rate And Site Of Release.
4. More Uniform Blood Concentrations.
5. Improved Patient Compliance.
6. Reduced Dosing Frequency.
7. More Consistent And Prolonged Therapeutic Effect.
8. A Greater Selectivity Of Pharmacological Activity.

Objectives[4]

Control Release Systems Include Any Drug Delivery System That Achieves Slow Release Of Drug Over An Extended Period Of Time.

The Objectives Of Oral Sustained Release Formulations Are:

1. Frequency Of Drug Administration Is Reduced.
2. Patient Compliance Can Be Improved.
3. Drug Administration Can Be Made More Convenient.
4. Better Control Of Drug Absorption Can Be Attained.

The Concept Of Targeting[5, 6]

The Concept Of Designing Specified Delivery System To Achieve Selective Drug Targeting Has Been Originated From The Perception Of Paul Elrich, Who Proposed Drug Delivery To Be As A "Magic Bullet". It Was The Very First Report Published On Targeting (Paul Elrich, 1902) Describing Targeted Drug Delivery As An Event Where A Drug-Carrier Complex/ Conjugate Delivers Drug(S) Exclusively To The Preselected Target Cells In A Specific Manner. Gregoriadis, 1981 Described Drug Targeting Using Novel Drug Delivery System As 'Old Drugs In New Cloths.

New Drug Delivery System Represents A Means By Which Drug May Be Continuously Delivered Either Locally Or Systemically Or A Larger Site In An Effective And Repeatable Manner. Controlled And Targeted Drug Delivery Systems Have Been Receiving More And More Attention As New Methods Of Drug Delivery.

One Of The Most Exciting Is The Target-Organ Oriented Drug Delivery System. Presenting Drugs Into Whole Body Is Not Only Wasteful But Also Likely To Lead To Harmful Effects That Can Be Eliminated If The Drug Is Delivered Only To Specific Target Organ. Targeted Delivery Is Not Restricted To Any One Route Of Administration. Oral Formulations, Parenterals, Transdermal And Pulmonary Route And Many Other Routes Are Available For Effective Drug Targeting.

Nanoparticles[8]

Nanoparticles Are Small Colloidal Particles Which Are Made Up Of Non-Biodegradable And Biodegradable Polymers. Their Diameter Is From 1-1000 Nm. One Can Distinguish Two Types Of Nanoparticles: Nanospheres, Which Are Matrix Systems And Nanocapsules, Which Are Reservoir Systems Composed Of A Polymer Membrane Surrounding An Oily Or Aqueous Core. These Systems Were Developed In Early 1970s. This Approach Was Attractive Because The Methods Of Preparation Of Particles Were Simple And Easy To Scale-Up. The Particles Formed Were Stable And Easily Freeze Dried. Due To These Reasons, Nanoparticles Made Of Biodegradable Polymers Were Developed For Drug Delivery. Indeed, Nanoparticles Were Able To Achieve With Success Tissue Targeting Of Many Drugs (Antibiotics, Cystostatics, Peptides And Proteins, Nucleic Acids, Etc.). In Addition, Nanoparticles Were Able To Protect Drugs Against Chemical And Enzymatic Degradation And Were Also Able To Reduce Side Effects Of Some Active Drugs.

Nanoparticles Are Used For Drug Targeting Both Active And Passive. The Relatively Small Size Of These Systems Limits Their Use, As Only Small Quantities Of Material Can Be Encapsulated. Other Types Of (Non-Biodegradable) Nanoparticle Systems Include Colloidal Sulfur And Colloidal Gold. Colloidal Sulfur Is Used As A Diagnostic Agent (Labeled With $^{99m}t_c$). It Is Usually Protected From Aggregation By The Addition Of Gelations As A Polymeric Stabilizer. Colloidal Gold Is Also Used As A Diagnostic (^{198}au) And As A Therapeutic Agent.

Biodegradable Polymers As Biomaterials[9]

The Last Two Decades Of The Twentieth Century Saw A Paradigm Shift From Biostable Biomaterials To Biodegradable (Hydrolytically And Enzymatically Degradable) Biomaterials For Medical And Related Applications.There Are Severalreasons For The Favorable Consideration Of BiodegradableoverBiostable Materials For Biomedicalapplications. The Major Driving Force Being Thelong-Term Biocompatibility Issues With Many Of Theexisting Permanent Implants And Many Levels Ofethical And Technical Issues Associated With Revisionsurgeries.

From The Pasttwo Decades Saw The Development Of A Range Of Newgeneration Synthetic Biodegradable Polymers Andanalogous Natural Polymers Specifically Developedfor Biomedical Applications. The Driving Force Is, Inpart, Due To The Emergence Of Novel Biomedicaltechnologies Including: Tissue Engineering, Regenerativemedicine, Gene Therapy, Controlled Drug DeliveryandBionanotechnology, All Of Which Require Biodegradable Platform Materials.

The Slow Evolution In The Development Ofbiodegradable Biomaterials Can Be Attributed Toseveral Unique Challenges In Developing Resorbableclinical Materials Compared To Developing Commoditypolymers. A Biomaterial Can Be Defined As Amaterial Intended To Interface With Biologicalsystems To Evaluate, Treat, Augment Or Replace Anytissue, Organ Or Function Of The Body. Theessential Prerequisite To Qualify A Material As Abiomaterial Is Biocompatibility, Which Is The Abilityof A Material To Perform With An Appropriate Hostresponse In A Specific Application. The Tissueresponse To An Implant Depends On A Myriad Offactors Ranging From The Chemical, Physical Andbiological Properties Of The Materials To The Shapeand Structure Of The Implant. In The Case Ofbiodegradable Biomaterials, Their Active Biocompatibilitymust Be Demonstrated Over Time.The Chemical, Physical, Mechanical And Biologicalproperties Of A Biodegradable Material Will Varywith Time And Degradation Products Can Be Producedthat Have Different Levels Of Tissue Compatibilitycompared To The Starting Parent Material.

MATERIALS

Simvastatin Provided By Sura Labs, Dilsukhnagar, Hyderabad, Ethyl Cellulosechemical Drug House, New Delhi, EudragitChemical Drug House, New Delhi, HpmcThomas Baker Pvt. Ltd., Mumbai., Span 60 Thomas Baker Pvt. Ltd., Mumbai, Distilled Water Rankem, Dichloromethane Rankem, Ethanol Rankem

METHODOLOGY

Analytical Method Development

Preparation Media

Preparation 0.2m Naoh Solution

8.0g OfNaoh Pellets Transferred In To 1000 Ml Of Purified Water And Mixed.

Preparation OfPh 6.8 Phosphate Buffer

Dissolved 6.8g Of Potassium Dihydrogen Phosphate In To 800ml Of Purified Water And Mixed Added 112 Ml Of 0.2m Naoh Solution And Diluted To Volume 1000ml With Purified Water And Mixed.

Determination Of Absorption Maxima

Absorption Maxima Are The Wavelength At Which Maximum Absorption Takes Place. For Accurate Analytical Work, It Is Important To Determine The Absorption Maxima Of The Substance Under Study.

For The Preparation Of Calibration Curve Stock Solution Was Prepared By Dissolving 100 Mg Of Accurately Weighed Drug In 100ml Of Dichloromethane (1mg/Ml). Further 1ml Of The Stock Solution Was Pipette Out Into A 100 Ml Volumetric Flask And Volume Was Made Up With Phosphate Buffer (Ph 6.8). From This Stock Solution Pipette Out 1ml And Dilute To 10 Ml With Phosphate Buffer And Subject For Uv Scanning In The Range Of 200-400 Nm Using Double Beam Uv Spectrophotometer. The Absorption Maxima Were Obtained At 235 Nm With A Characteristic Peak.

Preparation Of Calibration Curve

It Is Soluble In Dichloromethane; Hence Dichloromethane Was Used For Solubilizing The Drug. Stock Solution (1 Mg/Ml) Of Simvastatin Was Prepared In Dichloromethane And Subsequent Working Standards (5, 10, 15, 20 And 25 µG/Ml) Were Prepared By Dilution With Phosphate Buffer Of Ph-6.8. These Solutions Were Used For The Estimation Simvastatin By Uv Method. The Whole Procedure Was Repeated Three Times And Average Peak Area Was Calculated. Calibration Plot Was Drawn Between Concentrations And Peak Area. Calibration Equation And R^2 Value Are Reported.

Preparation Of Nanoparticles

Preparation Of Simvastatin Loaded Nanoparticles

Emulsification Solvent Evaporation Was Used To Synthesize Simvastatin Drug Loaded Polymeric Nanoparticles. Required Amount Of Ethyl Cellulose And Eudragit Rl100 (F1, F2, F3); Ethyl Cellulose And Hpmc- K100polymer (F4, F5, F6) Is Diffused In Ethanol (20 Ml) And Dichloromethane (1:1) Mixture. The Pre-Determined Amount Of Simvastatin Was Combined To The Polymeric Solution With Magnetic Stirring. Then The Suspension Was Injected Quickly Into Light Paraffin (100 Ml) Containing 2.5 Per Cent (V/V) Of Span 60, Thus Stirring To Result In A W/O Emulsion For 1 Min At 10,000 Rpm. The Residue Was Collected. N-Hexane (50 Ml) Was Used To Wash The Residue 2-3 Times. Then The Product Is Subjected To Drying For 24h At A Room Temperature.

Table 1: Composition Of Nanoparticles Formulations (F1 To F6)

Excipients	F1	F2	F3	F4	F5	F6
Simvastatin (Mg)	20	20	20	20	20	20
Ethyl Cellulose(Mg)	200	200	200	200	200	200
Eudragit (Mg)	100	200	300	-	-	-
Hpmc	-	-	-	100	200	300
Span 60 (Ml)	5	5	5	5	5	5
Distilled Water (Ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Dichloromethane (Ml)	10	10	10	10	10	10
Ethanol	15	15	15	15	15	15

All The Quantities Were In Mg

RESULT AND DISCUSSION

Preparation OfStandard Graph

Determination Of Absorption Maxima

The Standard Curve Is Based On The Spectrophotometry. The Maximum Absorption Was Observed At 235nm.

Calibration Curve

Graphs Of Simvastatin Was Taken In 6.8 Phosphate Buffer.

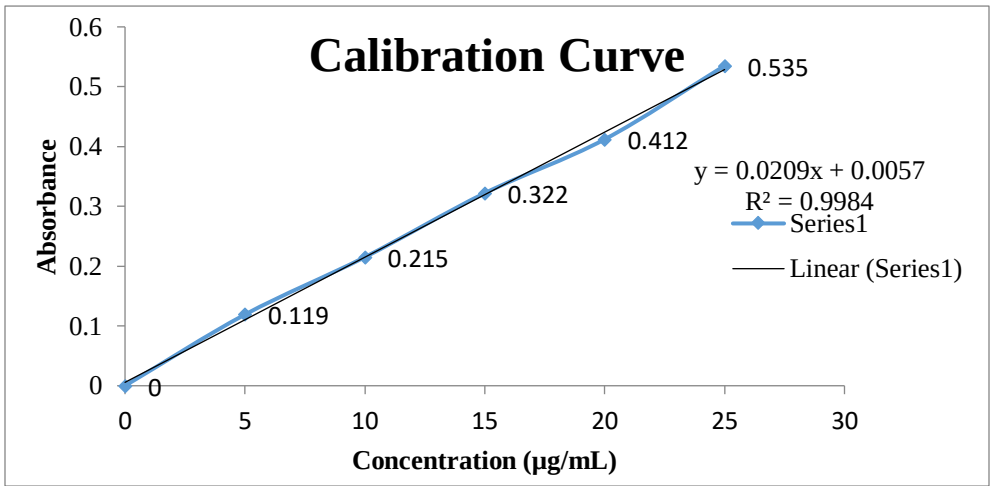

Fig 1: Standard Graph of Simvastatin InPh 6.8 Phosphate Buffer

Evaluation Of simvastatin Loaded Nanoparticles

Table 2: Evaluation of Nanoparticles

Batch No	Mean Particle Size(Nm)	%Yield	Drug Content	Drug Encapsulation Efficiency	Pdi	Zeta Potential (Mv)
F1	321.65	69.25	95.48	65.24	1.185	-23.12
F2	298.41	70.10	97.32	67.92	0.681	-29.05
F3	256.19	72.37	98.74	86.63	0.403	-32.92
F4	268.41	62.65	94.43	71.08	0.814	-25.16
F5	314.98	65.82	96.25	76.45	0.525	-27.76
F6	365.01	70.23	97.41	80.11	0.428	-30.07

In Vitro Drug Release Studies

Table 3:*In Vitro* Drug Release Studies Of Simvastatin

Time (Hr)	Cumulative Percent Of Drug Released					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	30.47	25.89	10.15	10.75	15.56	14.24
2	46.35	31.93	26.29	15.96	20.82	18.81
3	51.12	42.52	33.31	26.43	28.86	23.92
4	68.86	48.17	40.55	34.57	33.35	30.23
5	76.90	53.75	46.90	48.12	38.16	36.56
6	82.63	59.53	54.21	52.02	42.10	45.60
7	97.52	64.98	60.18	68.86	47.57	50.98
8		80.16	78.63	72.74	66.76	57.71
10		97.24	86.71	88.53	70.42	62.25
12			99.82	95.86	85.93	74.16

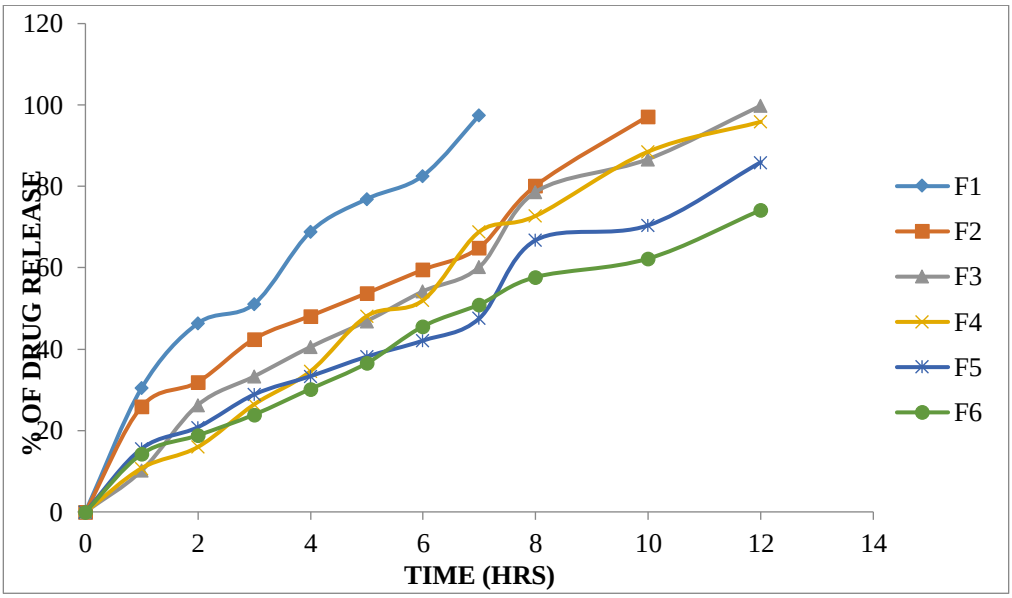

Fig 2: Dissolution Study of Simvastatin Nanoparticles

Table 4: Release Kinetics Data For Optimized Formulation (F3)

Cumulative (%) Release Q	Time (T)	Root (T)	Log(%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
10.15	1	1.000	1.006	0.000	1.954	10.150	0.0985	-0.994	89.85	4.642	4.479	0.163
26.29	2	1.414	1.420	0.301	1.868	13.145	0.0380	-0.580	73.71	4.642	4.193	0.449
33.31	3	1.732	1.523	0.477	1.824	11.103	0.0300	-0.477	66.69	4.642	4.055	0.586
40.55	4	2.000	1.608	0.602	1.774	10.138	0.0247	-0.392	59.45	4.642	3.903	0.739
46.9	5	2.236	1.671	0.699	1.725	9.380	0.0213	-0.329	53.1	4.642	3.759	0.883
54.21	6	2.449	1.734	0.778	1.661	9.035	0.0184	-0.266	45.79	4.642	3.578	1.064
60.18	7	2.646	1.779	0.845	1.600	8.597	0.0166	-0.221	39.82	4.642	3.415	1.227
78.63	8	2.828	1.896	0.903	1.330	9.829	0.0127	-0.104	21.37	4.642	2.775	1.867
86.71	10	3.162	1.938	1.000	1.124	8.671	0.0115	-0.062	13.29	4.642	2.369	2.273
99.82	12	3.464	1.999	1.079	-0.745	8.318	0.0100	-0.001	0.18	4.642	0.565	4.077

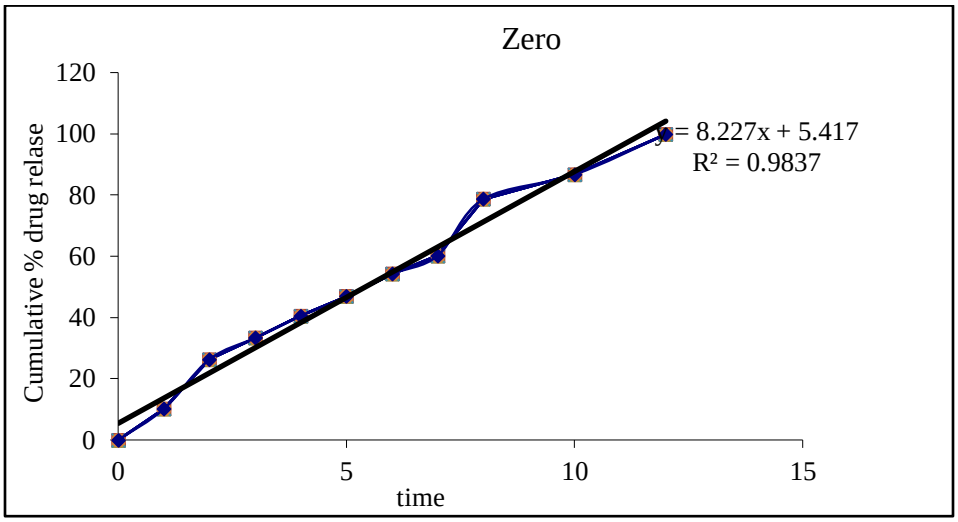

Fig3: Zero Order Release Kinetics Graph

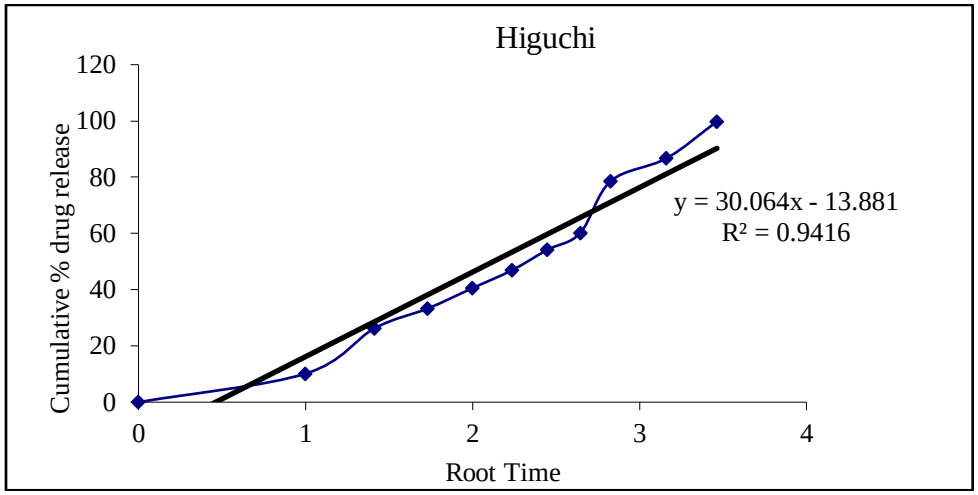

Fig 4: Higuchi Release Kinetics Graph

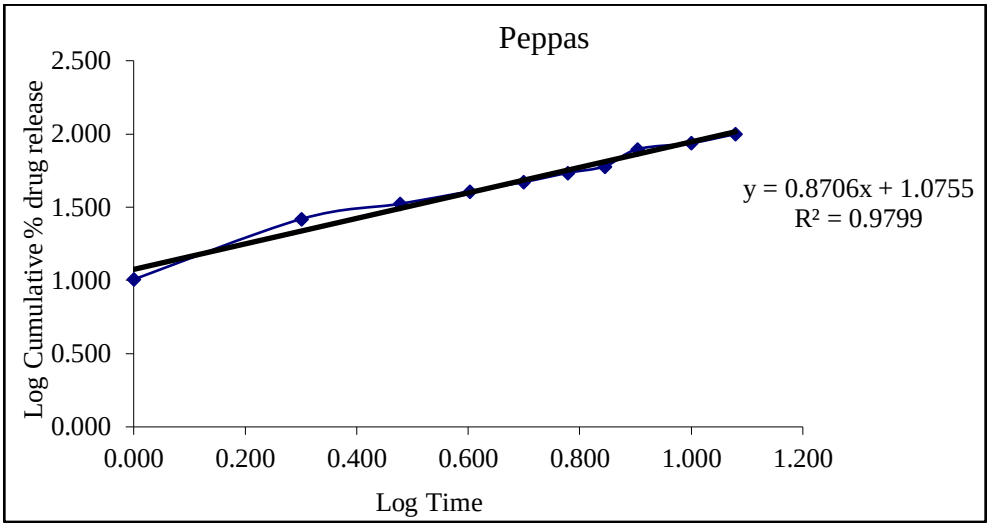

Fig 5: Peppas Release Kinetics Graph

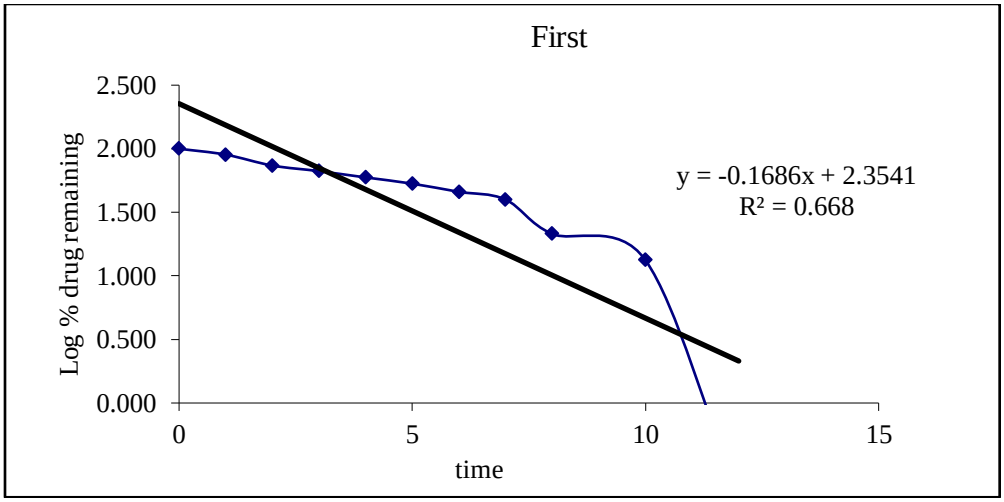

Fig 6: First Order Release Kinetics Graph

Drug – Excipient Compatibility Studies

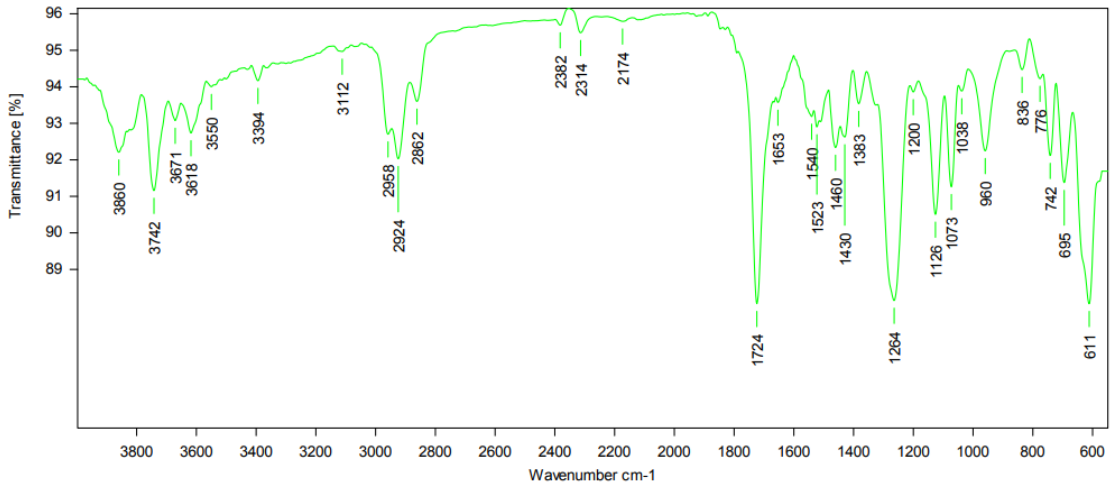

Fig 7: Ft-Tr Spectrum Of Simvastatin Pure Drug

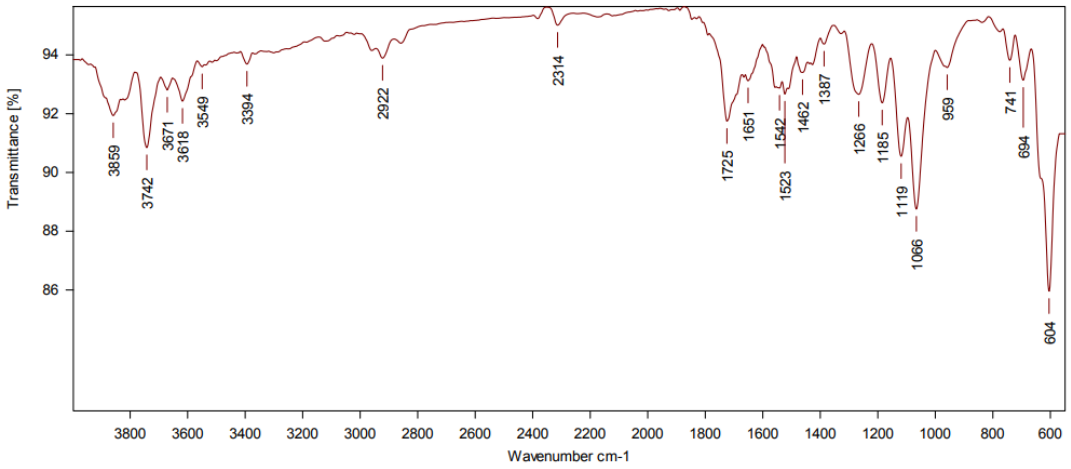

Fig 8: Ft-Ir Spectrum OfOptimised Formulation

Sem

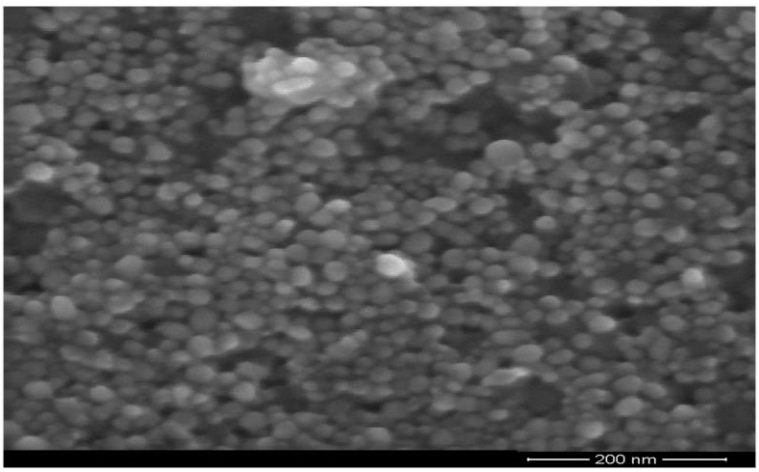

Fig 9: Sem Graph Of Optimized Formulation

Xrd

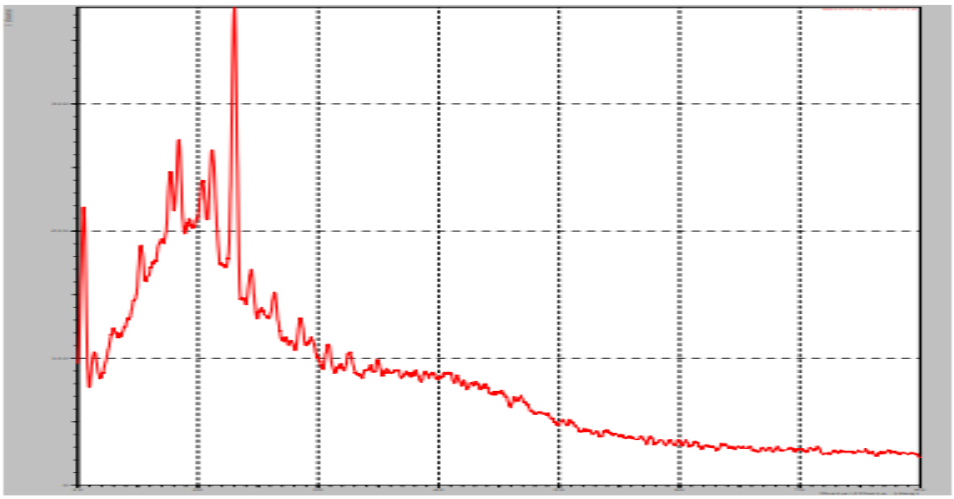

Fig9: Simvastatin F3 Optimised Formulation

CONCLUSION

The Present Work Aimed At Formulating Simvastatin Nanoparticle With Three Different Types Of Polymers Namely Ethyl Cellulose,Eudragit And Hpmc Using Emulsification Solvent Evaporation Method. This Method Was Simple And Cost Effective. Ftir And Uv Spectral Studies Authenticate The Spectra Obtained With The Sample Drug Matched With Standard Pure Drug. Uv Spectra Gave The Maximum Absorption Peak At 235nm.The Comparison Of Ftir Spectra Of Simvastatin And Mixture Of Simvastatin And Polymer Confirms That There Is No Appearance Of Additional New Peaks And disappearance Of Existing Peaks From That Of The Drug. This Indicates That There Is No Interaction Between The Drug And Polymer Used In The Study. Scanning Electron Micrograph Of The Prepared Nanoparticles at Different Magnification Showed That The Nanoparticles were Porous With A Smooth Surface Morphology And Spherical Shape. The Nano particlesporous Nature Of Nano particles was Clearly Observed In The Sem Images. Particle Size And Zeta Potential Was Determined By Malvern Zeta Sizer. The Particle Size Analysis Confirmed That The Prepared Sample Were In The Nanometer Range. Average Particle Size Obtained For The Formulations F1 And F6 Were 256.19nm And 365.01nm. Zeta Potential Values Of Nanoparticles indicated That The Formulated Nano particlesare Stable. The Amount Of Drug Being Entrapped In Nanoparticles was Calculated And All The Prepared Nanoparticles were Found To Possess Very High Entrapment Efficiency. From The *In-Vitro* Release Data From The Dialysis Bag Diffusion Method It Was Found That Formulations F3 Showed The Best Release Of 99.82% Respectively At The End Of 12 Hours. Increase Of Drug Release Was Observed As A Function Of Drug: Polymer Ratio. It Was Observed That The Drug Release Decreased With An Increase In The Amount Of Polymer For Each Formulation. This Is Because The Newly Developed Nano particlesis Believed To Exhibit A Core Structure With A Hydrophobic Core Formed By Ethyl Cellulose and Eudragit (F1-F3).The Data Obtained From The *In Vitro* Release Study Was Fitted To The Models Which Were Used To Find Out The Mechanism Of Drug Release From Simvastatin Nanoparticles. The *In Vitro* Release Model Best Fitted To Zero Order Release. The Simvastatin Nanoparticles Can Be Formulated By Cost Effective And Easy Emulsification Solvent Evaporation Method Using Hydrophobic Polymers Such As Ethyl Cellulose And Eudragit. The Formulated Simvastatin Nanoparticles Can Be Used In The Treatment Of Dyslipidemia Such As Atherosclerosis-Related Complications. This Can Be Targeted To The 3-Hydroxy-3-Methylglutaryl (Hmg) Coenzyme A Reductase And Produce Sustained Drug Delivery Which In Turn Reduces The Dose, Frequency Of Administration And The Side Effects.

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