



Freeze-Dried Simvastatin Dry Emulsion Tablets: Formulation, Characterization, And Evaluation

Deore Dipti Hiralal*, Pratik D. Patil, Avinash B. Gangurde, Krushna S. Chavan, Yash S. Bachhav, Nikita A. Pagar

KBHSS Trust's Institute of Pharmacy, Malegaon, Maharashtra, India.

Corresponding Author: Email: Deore Dipti Hiralal, KBHSS Trust's Institute of Pharmacy, Malegaon, Maharashtra, India.

Email: diptideore36851@gmail.com

Mobile No: 7720804956

Article History

Volume 6, Issue 14, 2024

Received: 25 June 2024

Accepted: 15 July 2024

doi:

[10.48047/AFJBS.6.14.2024.563-572](https://doi.org/10.48047/AFJBS.6.14.2024.563-572)

ABSTRACT:

This article describes the creation of dry emulsion tablets made using the dry emulsion technology to improve the performance of the poorly bioavailable medication simvastatin in vivo and in vitro. The lipid-lowering medication simvastatin prevents intestinal absorption of dietary and biliary cholesterol while leaving intact the absorption of nutrients that are soluble in fat. Simvastatin's very variable bioavailability is caused by its extremely low solubility and dissolution rate, which is partly attributable to substantial efflux by p-glycoprotein (P-Gp). The process of making tablets involved freeze-drying o/w emulsions of Simvastatin. A matrix former solution (alginate or gelatin, 2 or 4%), with sugar alcohol (mannitol) as the water phase and sesame oil as the oil phase under appropriate homogenization, was used to prepare the emulsions. Friability, disintegration time, and in-vitro dissolution of dry emulsion tablets were measured in the current investigation. The disintegration time was shown to be significantly influenced by the type of emulsifier and matrix forming. Studies on in vitro dissolution shown the increased dissolving rate of Simvastatin from freeze-dried pills in contrast to the standard medication. DSC analysis demonstrated that the manufactured tablets contained the medication in an amorphous form. The results obtained point to a possible, easily fabricated, and efficacious dosage form for the management of hyperlipidemia.

KEYWORDS: Simvastatin, lyophilized dry emulsion tablet, and hyperlipidemia, freeze drying, Sesame oil.

INTRODUCTION:

Oral forms are less expensive to produce than sterile formulations because they do not require a sterile environment. The main problem of oral drugs is low solubility, especially due to the low solubility of BCS Class II and IV drugs. ⁽¹⁾Simvastatin is an anti-hyperlipidemia drug that can lower blood cholesterol. Simvastatin, a hydroxymethylglutaryl-CoA reductase inhibitor, is the second drug to be studied in detail in humans. More than 1,800 patients with primary hypercholesterolemia were treated with the drug two years. Treatment at doses of 10 to 40

mg once daily can lower total cholesterol by up to 30%, reduce LDL cholesterol by 40%, and increase HDL cholesterol by approximately 10%.⁽²⁾

Simvastatin is an oral HMG-CoA reductase inhibitor that is authorised for use as a dietary supplement. It is the first semi-synthetic form of the statin lovastatin to receive FDA approval. Simvastatin aids in lowering issues related to dyslipidemia and the production of cholesterol. Excessive concentrations of low-density lipoprotein (LDL) cholesterol can cause arterial damage, which can result in heart attacks and strokes. However, there are several statins that are less harmful and more effective. By going over the indications, mechanisms of action, administration techniques, major side effects, contraindications, and monitoring of simvastatin in this exercise, doctors can collaborate as a team to manage patients' hyperlipidemia.⁽³⁾

Lyophilized dry emulsion tablet:

Several production processes, such as degradants, complex formation, or size reduction by Nano- or micronization, can increase the oral bioavailability of class II medicines. One of the greatest tactics is to make oral tablets (ODT) using multiple approaches. To increase simvastatin's oral bioavailability, dissolution rate, and solubility, a great deal of research has been done on the drug. The cyclodextrin complexes, solid dispersions, self-micro emulsifying system formulations, and micronization are among the topics covered in these investigations.⁽⁴⁾

There are issues with these techniques. Explosives have shown to be the most efficient method for enhancing the separation and bioavailability of poorly soluble active compounds since they are inexpensive, simple to employ, and highly effective.⁽⁵⁾ The efficiency and stability of sustained release of dry emulsions make them interesting. Dry emulsions provide a method of oral administration for lipophilic and poorly soluble drugs, as well as drugs that require protection from light or oxidation.⁽⁶⁾ LDET formulations should combine the advantages of lyophilized dosage forms and emulsions. The use of emulsion in drug preparation can improve the bioavailability and separation of water-insoluble drugs; On the other hand, freeze-dried materials have greater preservation, stability and rapid restructuring.⁽⁷⁾

Hyperlipidemia: Abnormal blood levels of one or all of the lipids or lipoproteins are called hyperlipidemia. This is the most common type of dyslipidemia, a term that encompasses all blood lipid abnormalities. Protein capsules carry water-insoluble substances called lipids. The density of the lipoprotein or capsule depends on its size. The fate of the product and its effect on metabolism depends on the density of lipoproteins it contains and the type of apolipoproteins. Some species can also cause pancreatitis in humans.⁽⁸⁾

MATERIALS AND METHODS:

Materials: Simvastatin was kindly donated by Swapnaroop Drugs and Pharmaceuticals, Aurangabad. Sesame oil was supplied from Kazima aromatics, Delhi. Gelatin, D-Mannitol and Glycine, Sodium alginate was provided from Vishal chemicals Mumbai.

Method:

Preparation of Simvastatin dry emulsion tablets

Simvastatin dry emulsion tablets were prepared as per Table No. 1 using either gelatin as the matrix former, a sugar alcohol (mannitol) and a collapse protectant (glycine). The emulsion was first prepared where mannitol and glycine were added to a solution of gelatin or alginate containing the surfactant, thus forming the aqueous phase. On the other hand, the oil phase was composed of 60 mg of Simvastatin solubilized in Sesame oil. The oil phase was then added to the aqueous phase containing matrix former, a sugar alcohol and a collapse protectant, under homogenization at 15,000 rpm for 5 min. Detailed formula of tablet is indicated in in table 1.

Table 1: Composition of Simvastatin freeze dried tablet

Sr.No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Simvastatin	40	40	40	40	40	40
2.	Gelatin	3	3.2	3.4	3.6	3.8	4
3.	Sodium alginate	2	1.8	1.6	1.4	1.2	1
4.	Mannitol	0.886	0.886	0.886	0.886	0.886	0.886
5.	Sesame oil	6	6	6	6	6	6
6.	MCC	83.114	84.914	88.114	86.114	89.614	85.114
7.	CCS	10	8.2	5	7	9.5	8
8.	Magnesium Stearate	5	5	5	5	5	5

Prepared emulsion was then transferred to a freezer at - 22°C and kept for 24 h. The frozen tablets materials were placed for 24 h in a LU-222 Advanced clabutima, Mumbai Freeze Dryer with a condenser temperature of -45°C and a pressure of 7×10^{-2} for 3 days. Then the freeze dried composition should be compressed into tablets by adding croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.⁽⁹⁻¹¹⁾

Characterization of dry emulsion tablets:

Uniformity of weight:

This test was performed in accordance with European Pharmacopoeia rules. Ten pills of each formula were weighed individually, and the average weight of the tablets was ascertained. The results are shown using the tablet mass's percentage relative standard deviation (% RSD).

Tablet friability:

The tablet friability test apparatus comprised a drum containing a set of six tablets. Following a four-minute rotation of the drum at 25 rpm, the tablets were removed, cleaned of any dust, and accurately weighed. The percentage of weight loss, regarded as a measure of friability, was calculated using the formula: Loss of weight: $(W1 - W2)/W1 \times 100$, where W1 represents the initial weight of the tablets before testing, and W2 represents the weight of the tablets after testing.

In-vitro disintegration time:

A DST-3 disintegration tester was used to measure the produced tablets' disintegration times in accordance with USP guidelines. The disintegration time was determined by measuring the amount of time that remained on the screen without any tablet fragments or just a small quantity of soft residue.

Determination of total Simvastatin content:

The simvastatin standard curve was used to calculate the total simvastatin content. Every tablet sample was precisely weighed (10 mg) and dissolved in enough methanol to equal a volume of 10 ml. Solutions were examined using a UV spectrophotometer set to 238 nm after being appropriately diluted with methanol. Triplicate runs of the experiments were conducted.

In-vitro Dissolution study:

Procedure: Using a paddle stirrer, the USP XXIII dissolution apparatus (Lab India) was used to study the in vitro dissolution of Simvastatin dry emulsion tablets. The dissolving medium utilised was 900 millilitres of pH 6.8 Phosphate buffer. Rotate speed of the stirrer was set to 50 rpm. Throughout the experiment, the dissolving media's temperature of $37 \pm 0.5^\circ\text{C}$ was kept constant, as previously advised. At predetermined intervals, the dissolution media was removed using a syringe equipped with a filter, and the absorbance at 238 nm was measured

to determine the drug release following an appropriate dilution with phosphate buffer. A new volume of dissolving liquid was added to the volume removed at each time interval. We computed and showed the percentage of Simvastatin released versus time.⁽¹²⁻¹⁷⁾

RESULTS AND DISCUSSION:

Appearance:

Simvastatin was found to be white, odourless, amorphous powder having bitter taste.

Melting point:

Melting of drug was found to be 133-135° c

Calibration curve:

Calibration curve of simvastatin was prepared in the range of 2 to 10 ppm. R^2 value of 0.9986 shows good linearity.

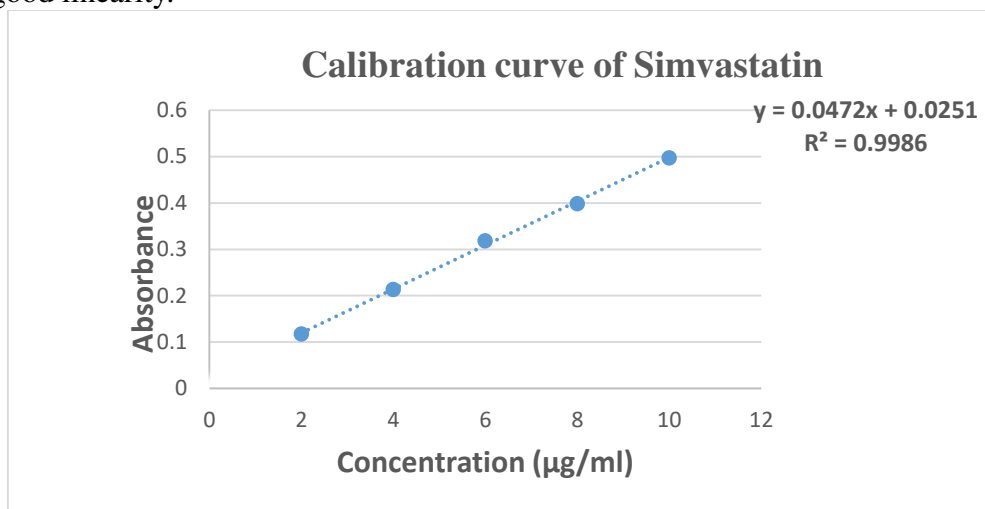
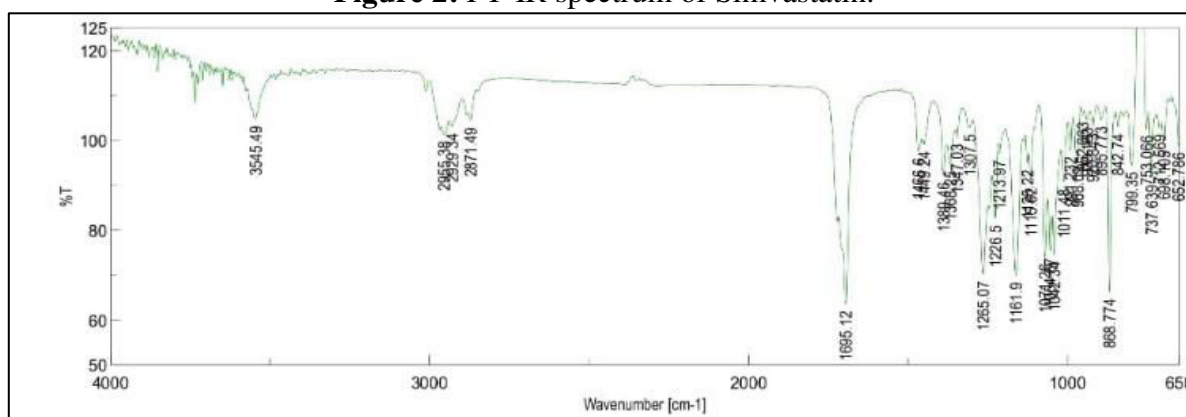


Figure 1: Calibration curve plot for Simvastatin.

Compatibility studies-FTIR:

To verify the interaction between the drug and polymers, the FTIR spectra of the Simvastatin and physical mixture of polymer were recorded. Simvastatin's distinctive peaks showed up in the physical mixture's spectrum with no discernible shift in location. It suggests that Simvastatin and the physical mixture of polymers did not interact. FTIR spectra of Simvastatin, physical mixture and sesame oil is indicated in figure 2, 3 and 4 respectively.

Figure 2: FT-IR spectrum of Simvastatin.



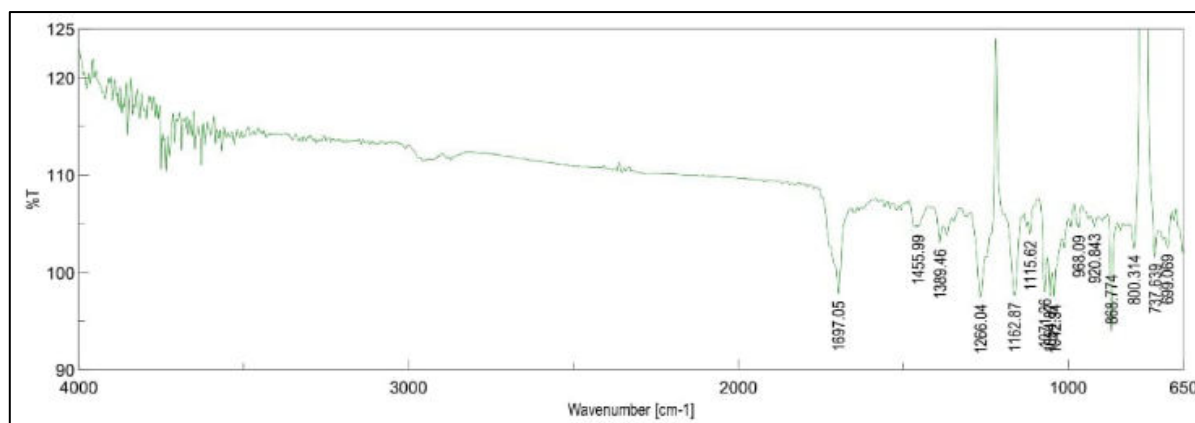


Figure 3:FT-IR spectrum of physical mixture

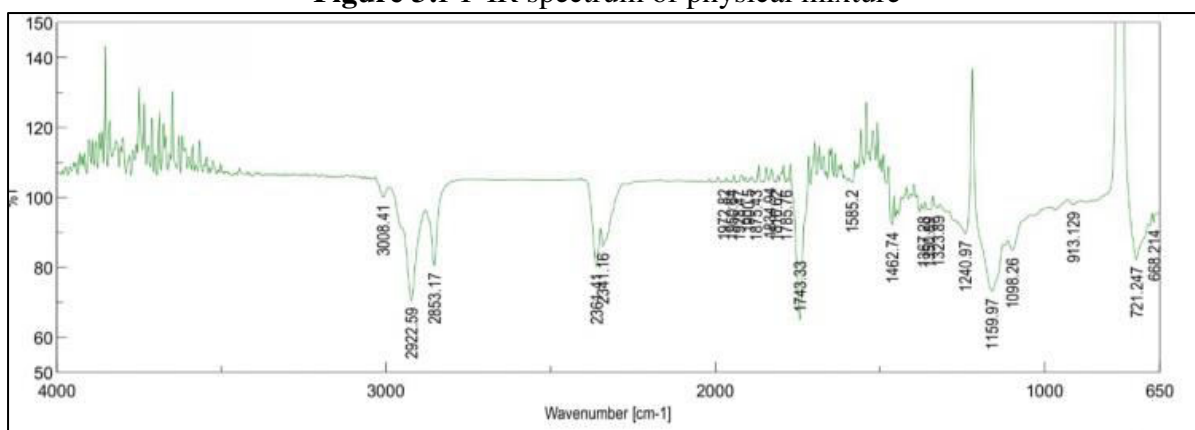


Figure 4:FT-IR spectrum of sesame oil

Differential Scanning Calorimetry(DSC):

The preferred method for pharmaceutical thermal analysis is often differential scanning calorimetry (DSC), which may yield comprehensive data on a material's energetic and physical characteristics. All processes that demand or create energy may be quantitatively detected with DSC (i.e., endothermic or exothermic phase transitions). The melting point of Simvastatin, at 139°C, is the location of its endothermic peak. Figure 5 indicates the DSC thermogram of simvastatin.

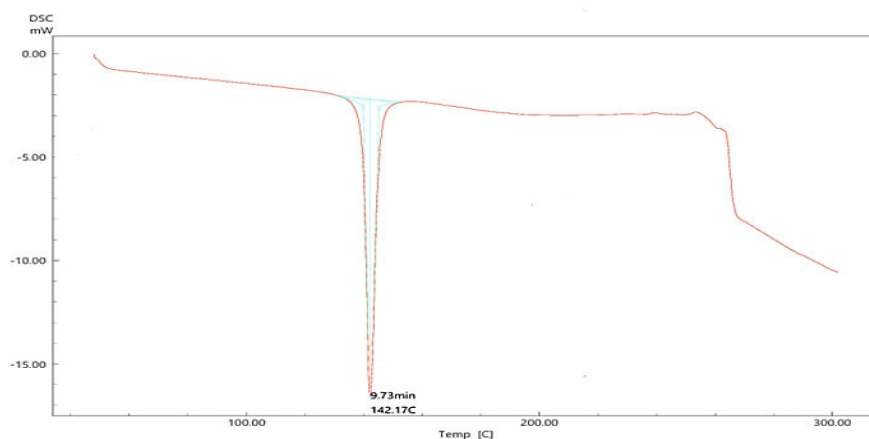


Figure 5:DSC Spectra of Simvastatin

XRD:The XRD diffractogram of lyophilized simvastatin showed reduced peak intensities at different diffraction angle, suggesting the amorphous characteristics. XRD spectra of simvastatin is indicated in figure 6.

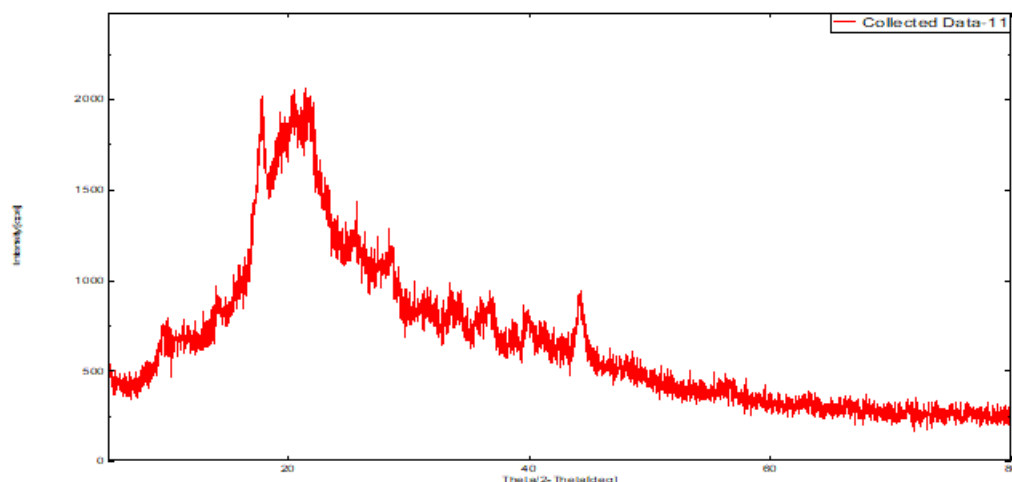


Figure 6:XRD graph of lyophilized Simvastatin drug

Evaluation of tablet:

Prepared tablets were evaluated for various parameters like weigh uniformity, % of friability, drug content, and disintegration time. Results of the study are indicated in table 2.

Table 2:Evaluation parameters of tablets.

Formulation	Uniformity of weight(% RSD)	Friability (%)	Total Simvastatin content (%)	Disintegration time(s)
F1	0.65 ± 0.11	0.65 ± 0.12	98.4 ± 0.24	150
F2	0.69 ± 0.25	0.66 ± 0.21	96.11 ± 0.56	148
F3	0.71 ± 0.21	0.59 ± 0.11	95.21 ± 1.9	154
F4	0.69 ± 0.24	0.70 ± 0.45	96.77 ± 0.24	121
F5	0.72 ± 0.25	0.52 ± 0.47	97.11 ± 0.27	115
F6	0.75 ± 0.32	0.46 ± 0.38	99.08 ± 0.24	100

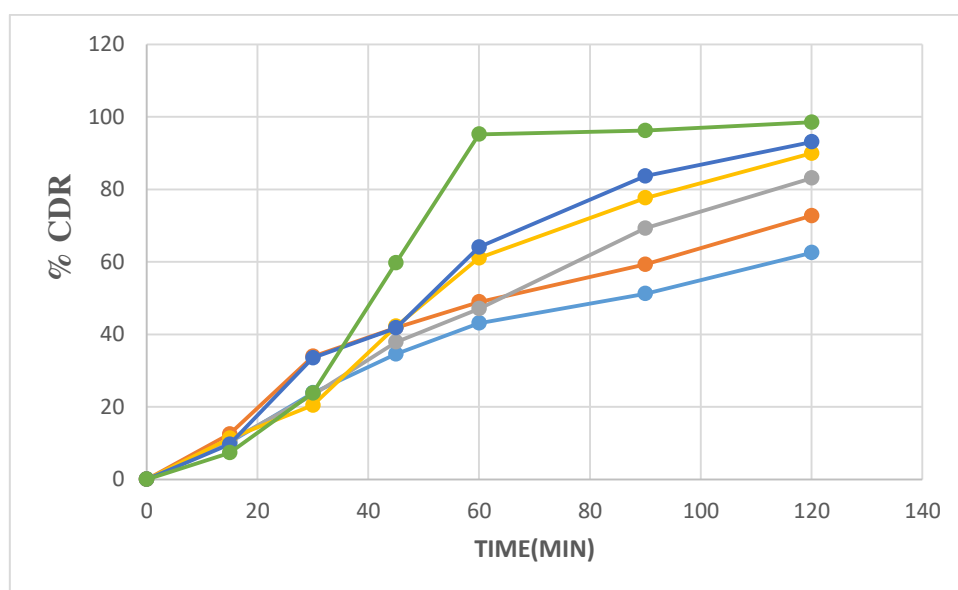


Figure 7:Dissolution profile of various batches tablets in pH 6.8 Phosphate buffer.

Dissolution profiles of prepared tablets are indicated in figure 7.

Kinetics of Drug Release:

Table 3: Kinetic parameters of Simvastatin dry emulsion tablets.

Time (min)	Sq. root of time	Log time	% CDR	% Cum drug unrelease	Log Cum drug unrelease	Log % CDR	Cube root of % drug unrelease
0	0	∞	0	100	2	∞	4.642
15	3.8729	1.176	7.35	92.65	1.9668	0.8662	4.5249
30	5.4772	1.4771	23.79	76.21	1.882	1.3763	4.2397
45	6.7082	1.6532	59.75	40.25	1.6047	1.7763	3.427
60	7.7459	1.7781	95.25	4.81	0.6821	1.9785	1.688
90	9.4868	1.9542	96.2	3.8	0.5797	1.9831	1.5604
120	10.9544	2.0791	98.48	1.52	0.1818	1.9933	1.1497

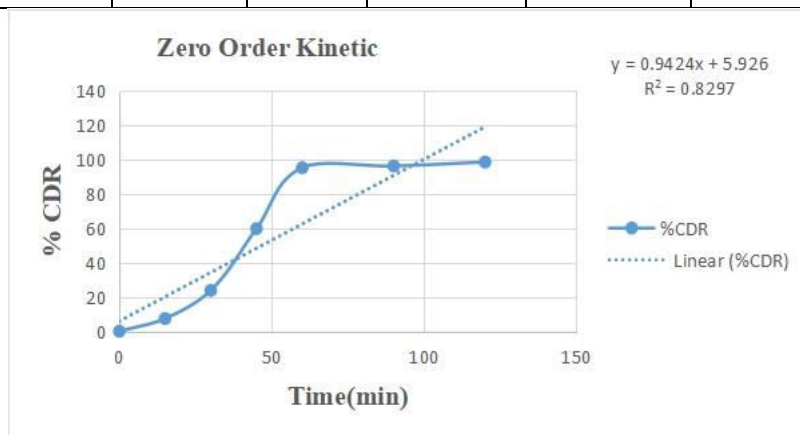


Figure 8:Zero order drug release kinetic

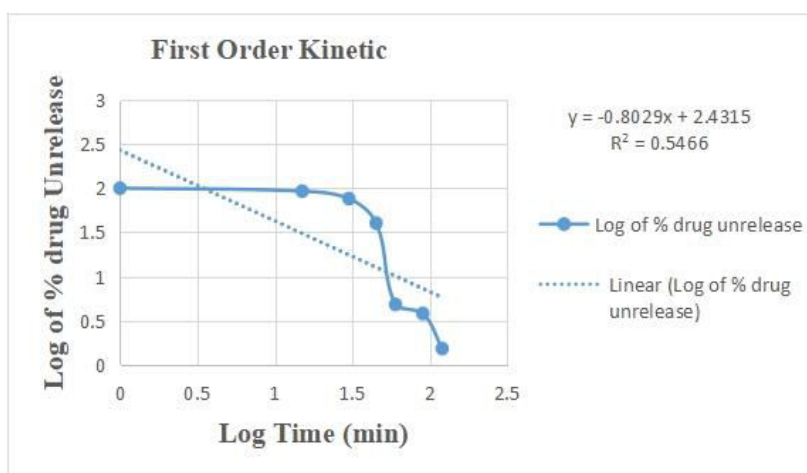


Figure 9:First order drug release kinetic

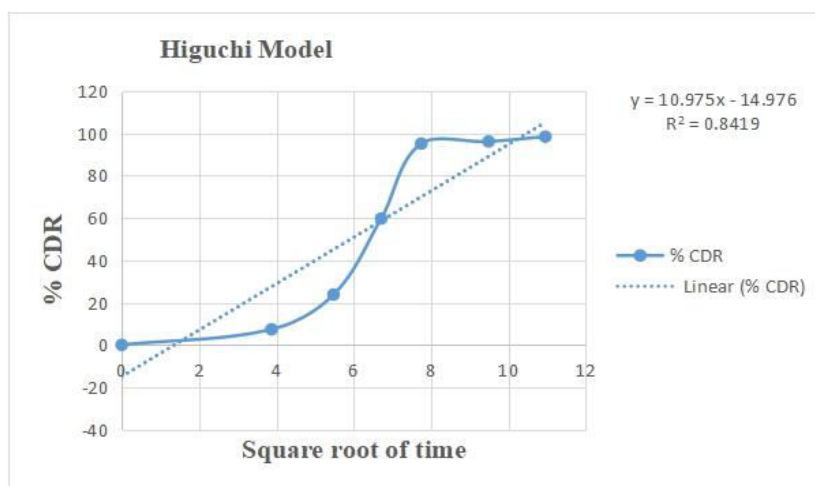
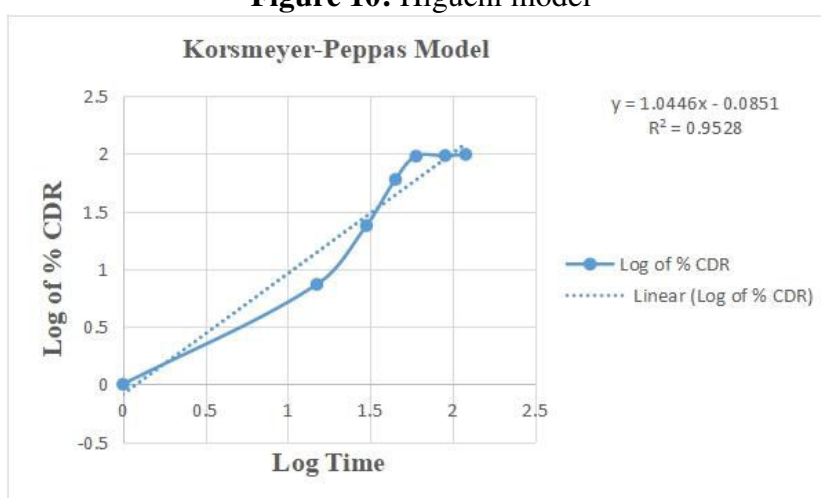
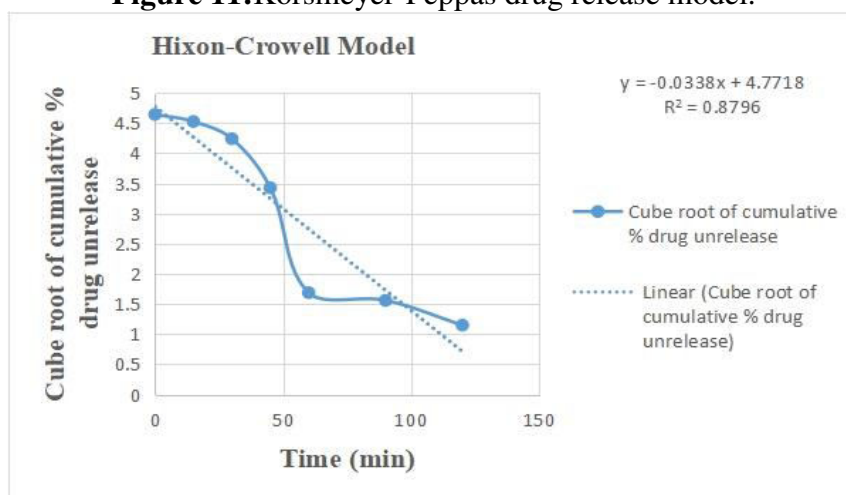
**Figure 10: Higuchi model****Figure 11:Korsmeyer-Peppas drug release model.****Figure 12:Hixon-Crowell drug release model**

Table 4: Different kinetic models and their regression coefficient (R^2)

Sr. No.	Release Kinetic Models	Regression Coefficient (R^2)
1	Zero Order	0.8297
2	First Order	0.5466
3	Higuchi Model	0.8419
4	Korsmeyer-Peppas Model	0.9528
5	Hixon-Crowell	0.8796

The release data of optimized batch F6 was fitted to various mathematical models such as Zero order, first order, Higuchi model, Korsmeyer- Peppas model and Hixcon-Crowell model to evaluate the kinetics of drug release. Thus according to the obtained values, the best release was found to be fitted in Korsmeyer-Peppas Model, leads to diffusion drug release mechanism.

DISCUSSION:

A binding agent is a crucial component of the LDET formulation since it lowers the drug's surface tension and makes the tablets harder. Gelatin serves as both a matrix forming and a binder for freeze-dried tablets in the current formulation. Additional excipients, such as sugar alcohol, provide the lyophilized matrix a porous structure and hence improve the formulation's solubility. Because the dosage form's porous shape makes it difficult to handle, gelatin or other excipients can be evaluated as a binder to affect freeze-dried tablets. All prepared tablets were acceptable weight variation values as indicated by the relative standard deviation (RSD) of the tablet mass which ranged from 0.65 to 0.75%. Tablet friability was determined by Roche Friabilator and weight loss was calculated and presented in terms of % friability. From table we can say that percentage weight loss of tablets of each formulation was found in the range 0.44 ± 0.38 to 0.65 ± 0.12 . It had found that the disintegration time of all tablet batches is ranging from 100 to 150 Seconds. The total Simvastatin content was found to be uniform along all formulation and ranged from 95.21 ± 1.9 to 99.08 ± 0.24 . The Simvastatin dry emulsion tablet's in-vitro dissolving study reveals a noteworthy percentage drug release in formulation F6, which is caused by a higher percentage of gelatin, which both increases the drug molecule's hydrophilicity and lowers its surface tension.

REFERENCES:

1. Bashir, M. A. (2023). Development and evaluation of self-emulsifying drug-delivery system-based tablets for simvastatin, a BCS class II drug. *Drug design, development and therapy*. 17,261–272. doi: 10.2147/dddt.s377686.
2. Mauro, V. F. and MacDonald, J. L. (1991). Simvastatin: A Review of its Pharmacology and Clinical Use. *DICP: the annals of pharmacotherapy*. 25(3), 257–264. doi: 10.1177/106002809102500309.
3. Aceves-Hernández, J. M. (2011). Solubility of simvastatin: A theoretical and experimental study. *Journal of molecular structure*. 995(1–3), 41–50. doi: 10.1016/j.molstruc.2011.03.048.
4. Sastry, S. V., Nyshadham, J. R. and Fix, J. A. (2000). Recent technological advances in oral drug delivery – a review. *Pharmaceutical science & technology today*. 3(4), 138–145. doi: 10.1016/s1461-5347(00)00247-9.
5. Usman, M. J. and Ahmadu Bello University zaria. (2017). Fabrication and characterization of ezetimibe solid dispersion for solubility enhancement. *Universal journal of pharmaceutical research*. 2(1),12–16. doi: 10.22270/ujpr.v2i1.r3.

6. Niczinger, N. A. (2017). Physicochemical analysis in the evaluation of reconstituted dry emulsion tablets. *Journal of pharmaceutical and biomedical analysis*. 134,86–93. doi: 10.1016/j.jpba.2016.11.031.
7. Corveleyn, S. and Remon, J. P. (1998). Formulation of a lyophilized dry emulsion tablet for the delivery of poorly soluble drugs. *International journal of pharmaceuticals*. 166(1),65–74. doi: 10.1016/s0378-5173(98)00024-6.
8. Kastelein, J. J. P. and Sankatsing, R. R. (2005). Ezetimibe/simvastatin in the treatment of hyperlipidaemia: Treatment of Hyperlipidaemia. *International journal of clinical practice*. 59(12),1464–1471. doi: 10.1111/j.1368-5031.2005.00737.x.
9. Chandrasekhar, R. (2009). The role of formulation excipients in the development of lyophilised fast-disintegrating tablets. *European journal of pharmaceuticals and biopharmaceutics*. 72(1),119–129. doi: 10.1016/j.ejpb.2008.11.011.
10. D. Madhuri, K. Naga Raju, R. China Babu, SD. (2016). Design, Development and Evaluation of Dry emulsion of Cephalexin Monohydrat. *International Journal of Pharmaceutical Sciences Review and Research*, 39(2),276–280.
11. Gunjan Subedi, Basanta Dhodary, Basanta Rijal. (2015). Development, Optimization and In-Vitro Evaluation of Aceclofenac Dry Emulsion Tablets by Carrier Based Technique. *International journal of pharmacy and pharmaceuticals*. 5(1), 239–252.
12. Ahmed, I. S. and Aboul-Einien, M. H. (2007). In vitro and in vivo evaluation of a fast-disintegrating lyophilized dry emulsion tablet containing griseofulvin. *European journal of pharmaceutical sciences*. 32(1),58–68. doi: 10.1016/j.ejps.2007.05.114.
13. Salama, A. H., Basha, M. and El Awdan, S. (2018). Experimentally designed lyophilized dry emulsion tablets for enhancing the antihyperlipidemic activity of atorvastatin calcium: Preparation, in-vitro evaluation and in-vivo assessment. *European journal of pharmaceutical sciences*. 112, 52–62. doi: 10.1016/j.ejps.2017.11.003.
14. Ravi. Srinu, M. Teja Krishna, V. Sai Kishore, K.V.S. Prasada Rao (2013). Formulation and evaluation of fast dissolving tablets of simvastatin using novel co-processed superdisintegrants. *Scholars Academic Journal of Pharmacy*. 2(4),340–353.
15. Jadhav, SP. Patil, DM. Sonawanem DD. (2023). Formulation of Tablet of Ivermectin Co-Crystal for Enhancement of Solubility and Other Physical Properties. *Journal of Pharmaceutical Negative Results*. 14(1),513–520.
16. Jadhav, K. Jadhav S. (2021). Mouth Dissolving Film of Domperidone: An approach towards Formulation and its Evaluation. *Journal of pharmaceutical research international*. 33(44A),140–150. doi: 10.9734/jpri/2021/v33i44a32600.
17. Jadhav, S. P. (2024) Effect of Lyophilization on Characteristics of Iloperidone Nanosuspension. *International journal of drug delivery technology*. 14(02),1039–1043. doi: 10.25258/ijddt.14.2.65.