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Development And Evaluation Of Dry Syrup Of Class II Drug Using Solid Dispersion Approach

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ABSTRACT:

Solubility and dissolution is the rate limiting step for absorption and bioavailability of BCS class II drugs. Simvastatin (SMV) has been chosen as the model medication in this work in order to develop and evaluate the dry syrup utilizing a solid dispersion (S.D.) method. Using a solvent evaporation technique, this study created solid dispersions of simvastatin using sugar-based carriers such as xylitol, sorbitol, lactulose, and one non-sugar carrier called soluplus. Various suspending agents were utilized to transform optimized Simvastatin S.D.s into dry syrup formulations. The dry syrup formulations were assessed for flow characteristics, drug content, and reconstitution time. The reconstituted syrup underwent tests for viscosity, dispersibility, pH, sedimentation volume, degree of flocculation, drug release studies, and accelerated stability testing, scanning electron microscopy were used to characterize the dry syrup. SMV:Lactulose (1:1.5) selected as optimized SD and incorporated into dry syrup. Good flow properties were demonstrated by SMV dry syrup formulations, which are crucial for filling the container. The formulations were found to take between 3.2 and 5.2 minutes for reconstitution; good redispersibility (8 to 15 strokes); their pH ranged from 6.3 to 6.6; their sedimentation volume was determined to be between 0.45-0.95; and over the course of an hour, all of the formulations demonstrated 99% drug release. On the other hand, the drug release from the marketed tablet dosage forms was only 56% after an hour. The optimized formulation (F9) subjected for accelerated stability testing by following the ICH stability guidelines. From the results obtained it is concluded that formulation (F9) is an optimized formulation with good stability and following first order kinetics of drug release.

KEYWORDS: *Simvastatin; dry syrup, stability testing, redispersibility, sedimentation volume.*

INTRODUCTION :

The relative bioavailability of a drug's formulation can be improved using solid dispersion, one of the most effective methods for increasing the rate at which poorly water-soluble drugs dissolve. Solid dispersions are generally prepared by using the solvent evaporation approach and the fusion method. Additional grinding, sieving, mixing, and [1]granulation are typically required to produce the various needed formulations.

Liquid dose forms are necessary because many patients, particularly those who are young and elderly, have trouble swallowing solid dosage forms (1).

Therefore, it will be best to formulate a suspension of medications that are marginally soluble in water. However, the final result might need more chemically and physically stable.

The current effort aims to provide a dry syrup-based reconstitution of the suspension

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dosage form (1). Commercial dry combinations known as "dry syrups" need water added when they are being dispensed.

Drugs, colors, flavours, sweeteners, stabilizers, and preservatives—all of which may be required to improve the formulation's stability—are used in the commercial preparation of the dry syrup.

The medication, colorants, sweeteners, stabilizing agents, viscosifying agents, and preserving agents that might be required to improve the stability of formulation are all included in the commercially prepared dry mix of oral suspension. The sachets' grains need to be consumed as a dispersion in a glass with the recommended volume of distilled water. It is advised that the dry oral suspension be ingested right after preparation, despite studies showing that the suspension is stable for 24 hours after formulation in a liquid (2,3). One of the key factors influencing patient compliance is taste. One of the many significant formulation issues with some medications is an unpleasant taste(4).

Because Simvastatin (SMV) is a crystalline drug with almost negligible water solubility, it has a low rate of absorption from the Gastro Intestinal (GI) tract (5). It is an effective and selective inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the enzyme that converts HMG CoA into mevalonate. Simvastatin inhibits a critical step of the liver's cholesterol production when combined with food to treat dyslipidemia and hypercholesterolemia. The cytochrome-3A system in the liver breaks down Simvastatin from its oral form into its b-dihydroxy acid form, or simvastatin acid, which disrupts the rate-limiting step in the creation of cholesterol(6,7). The chemical structure of SMV is shown in Figure 1.

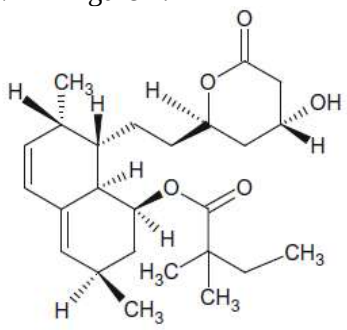

Figure 1: Chemical structure of Simvastatin (SMV)

In the present work, SMV pediatric dry syrup formulations were developed using the solid dispersion technique and subjected to various evaluation tests.

MATERIALS AND METHODS:

Materials:

Simvastatin (Aurobindo Pharma Ltd., Hyderabad), lactulose, Sorbitol, xylitol, lactulose, and soluplus were used as carriers for solid dispersions. Gellan gum, Guar gum, CMC (Carboxy Methylcellulose), Sodium Starch Glycolate, Sodium benzoate, Sodium citrate, Sucrose, Sodium Lauryl Sulfate, KBr, Aerosil, Flavor, Quinoline yellow were selected as excipients for dry syrup.

Methods:

The Simvastatin Solid Dispersions (S.D.) were developed with sugar carriers, including xylitol, Sorbitol, lactulose, and soluplus. The developed S.D.s were evaluated, and the formulation containing Simvastatin (1 part): lactulose (2 parts) was selected as the optimized composition of the drug-to-carrier ratio and used for the development of dry syrup formulation (8).

Development of dry syrups for Simvastatin using optimized S.D.s:

The optimized S.D. was formulated into a dry syrup formulation. The formulation of dry syrup is given in Table 1.

Table 1: Formulation of Simvastatin Dry Syrup

Ingredients (%w/v)	Batch code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Simvastatin + Lactulose	40	40	**40**	40	40	**40**	40	40	**40**
Gellan gum	1	1.5	**2.0**	-	-	-	-	-	-
Guar gum	-	-	-	1.0	1.5	**2.0**	-	-	-
CMC (Carboxy Methylcellulose)	-	-	-	-	-	-	1.0	1.5	**2.0**
Sodium Starch Glycolate	10	10	**10**	10	10	**10**	10	10	**10**
Sodium benzoate	2.1	2.1	**2.1**	2.1	2.1	**2.1**	2.1	2.1	**2.1**
Sodium citrate	2.1	2.1	**2.1**	2.1	2.1	**2.1**	2.1	2.1	**2.1**
Sucrose	24.0	24.0	**24.0**	24.0	24.0	**24.0**	24.0	24.0	**24.0**
Sodium Lauryl Sulfate	1.1	1.1	**1.1**	1.1	1.1	**1.1**	1.1	1.1	**1.1**
KBr	0.06	0.06	**0.06**	0.06	0.06	**0.06**	0.06	0.06	**0.06**
Aerosil	5.2	5.2	**5.2**	5.2	5.2	**5.2**	5.2	5.2	**5.2**
Flavor	q.s	q.s	**q.s**	q.s	q.s	**q.s**	q.s	q.s	**q.s**
Quinoline yellow	q.s	q.s	**q.s**	q.s	q.s	**q.s**	q.s	q.s	**q.s**
Total (gm)	10gm	10gm	**10gm**	10gm	10gm	**10gm**	10gm	10gm	**10gm**
Reconstitute with water up to 30 ml									

In order to ensure perfect mixing in a pestle and mortar, all the ingredients were accurately weighed and combined using the geometric dilution method. In order to achieve uniform mixing, the finished mixture was vigorously combined in a pestle and mortar.

Evaluation of Dry syrups

Physical Appearance and Flow Properties

Prepared formulations were subjected to determine color, odor, appearance, and derived properties of powders like Carr's index, Hausner's ratio and angle of repose, bulk density, and tapped density (9,10,11).

Drug content uniformity:
A precise weight of 5 mg of dry syrup powder was measured and it was dissolved in 100 milliliters of 0.1 N HCL. We gave the solution a good shake. By passing the material through Whatman No. 41 filter paper, the undissolved material was eliminated. Next, dilute the mixture to yield 10µg of solution. At 237 nm, the diluted solutions' absorbance was measured. (12).

Reconstitution Time
1 ml of demineralized water was introduced into the vial through the rubber cap to reconstitute the dry syrup that had been produced. The contents of the vial were then thoroughly mixed by giving it a vigorous shake.

Evaluation of Reconstituted Dry Syrup Formulation

Sedimentation behavior

Redispersibility:
After the formulations were held for seven days, the redispersibility was measured by counting the number of strokes needed to redisperse the produced sediment (not more than 100 strokes = Redispersibility).
Sedimentation Volume Ratio:

A 50 milliliters of each suspension were kept undisturbed at room temperature in a stopper measuring cylinder in order to calculate the sedimentation volumes. Evident liquid separation was seen at intervals of one day to fourteen days.
The sedimentation volume F was calculated using the formula
$F = Vu/Vo,$
where Vu is the sediment volume and Vo is the sample's initial height. It is explained in percentage terms.
(13, 14).

Degree of flocculation (β)
$\beta = F/F\infty$
$= (Vu/Vo)/ (V\infty/Vo)$
$= Vu/V\infty$
= Ultimate sediment volume of flocculated suspension/ Ultimate sediment volume of deflocculated suspension.

Determination of pH
Traditionally, the pH value has been used to indicate whether an aqueous solution is acidic or alkaline. Using a glass electrode and potentiometry, the pH of a solution was calculated. A digital pH meter was permitted to stabilize it. After that, buffer tablets were used to standardize the pH meter. The pH meter contained the suspension formulation. The reading was recorded when the pH meter didn't fluctuate (13).

Viscosity:
Viscosity was measured using the steady shear method to identify the rheologic properties of the created suspensions, namely the "non-Newtonian viscosity." An RVT Brookfield viscometer from Choksi Lab was used to measure the rheology of every suspension (Indore, M. P.) Following the suspension's complete thixotropy elimination, all measurements were carried out (15).

In-vitro dissolution studies

DISSO 2000, Lab India was used to measure the in-vitro dissolution rate of simvastatin dry syrups from their reconstituted syrup on the first and seventh day. apparatus for an 8-station dissolution rate test using a USP type II paddle stirrer running at 50 rpm. The dissolution medium, which was kept at 37±0.5oC, included 900 cc of 0.1 N HCl. To each dissolving vessel, 100 mg of reconstituted syrup containing simvastatin was added. Five milliliter aliquots of the dissolving medium were extracted at intervals of five, ten, fifteen, thirty, forty, and sixty minutes using a 0.45 µ nylon disc filter. Every time, a new sample of dissolving fluid was added to the one that had been removed. With the use of 0.1N HCl to dilute the filtered sample solution appropriately, the amount of drug released was measured using a UV spectrophotometer by measuring the sample's absorbance at 237 nm. (16).

Kinetics Of Drug Release

Using zero order and first order methods, the drug release mechanism for the Simvastatin dry syrups was identified (17).

The following forms of data handling were used to depict the in vitro release profile results for each formulation:1. Cumulative percentage of medication released vs time using a zero-order kinetic model.

2. Log cumulative percent of medication remaining vs time in a first-order kinetic model.

Zero-Order Kinetic

It explains the mechanism wherein the medication release rate is unaffected by concentration.

$$Qt = Qo + Ko\ t$$

Where,

Qt= Amount of drug dissolved in time t

Qo = Initial amount of drug in the solution, which is often zero

and

Ko = zero order release constant.

When the zero-order drug release kinetic is followed, a straight line with a slope of Ko and an intercept at zero can be seen when Qt is plotted against t.

First Order Kinetic

It explains how drugs are released from systems where the rate of release is dependent on concentration.

$$\text{Log } Qt = \log Qo + kt/\ 2.303$$

Where,

Qt = amount of drug released in time t.

Qo = initial amount of drug in the solution k = first order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Qo- Qt) versus t will be a straight line with a slope of kt/ 2.303and an intercept at t=0 of log Qo.

Accelerated stability study

Simvastatin's physicochemical properties rely on the excipients used in its manufacture, hence its chemical stability is crucial. Therefore, stability investigations were conducted on the preparations. By calculating the proportion of the starting concentration that remained after a given amount of time and under various circumstances, the stability of simvastatin was evaluated. A significant alteration in medication stability was defined as a concentration difference of ± 10%. Based on the quantity of constituents in the formula, the concentration of Simvastatin in suspension should be 40 mg/ml. Results for investigations on drug content and in vitro dissolution have been presented. Stability tests on dry syrups were carried out for three months at 40 ± 2˚C and 75 ± 5% R.H. (18).

Particle size and Surface Characterization

The dry syrup was scanned using a scanning electron microscope to know the surface characteristics.

RESULTS AND DISCUSSION:

Evaluation studies of Dry Syrup:

Physical Appearance and Flow Properties:
Quinoline yellow was utilized as a coloring ingredient and strawberry flavor was included in all of the formulations. The granulation method was used to create the dry suspension. Every formulation, ranging from F1 to F9, was seen as a powder.

Flow properties of dry syrup:
Different formulations' angles of repose were < 22.34±1.28, indicating that the material has good flow characteristics. Thus, the free-flowing nature of blends' flow feature was verified. The blend's bulk density was determined to range from 0.412±1.28g/cm3 to 0.470±1.36 g/cm3. A taped density of 0.524±2.01 g/cm3 to 0.572±1.87 g/cm3 was discovered. These numbers show that the blends' flow characteristics were favorable. The results show that the blends have good flow character. Carr's index for all the formulations was found to be between 14.27±1.28-16.93±1.39 and Hausner's ratio from 1.21±1.58-1.39±2.08..

Drug content:
The drug content of formulation F1-F9 was found to be between 98.14±1.74-100.21±1.87. This indicates all formulations exhibit good content uniformity.

Viscosity:
The Viscosity of all reconstituted dry syrup formulations was determined using the steady shear method with an RVT Brookfield viscometer, and the Viscosity of formulations was found to be between 451**±9** cps and -1474**±**4 cps.
Table 2 displays the Viscosity of the various formulas. Among the three suspending agents, CMC exhibited the highest Viscosity. Thus, the high Viscosity of the suspending agent CMC was the source of the higher sedimentation volume and improved redispersibility.
Since the suspension's Viscosity was higher, the solid particles within it would not settle for an extended period of time. They will, therefore, continue to be suspended. This resulted in a slower rate of sedimentation and a more significant amount of suspension sedimentation.

Redispersibility:
The total strokes needed for various formulations can be used to determine the suspension's redispersibility. The formulation batch F9 (CMC 3%), in comparison to all other formulations, had the fewest number of strokes (8), according to the results. Thus, the findings indicated that the formulation containing 3 percent CMC was readily distributable. This was due to the fact that the same formulation's sedimentation volume was higher than that of any other formulation.

Table 2: Evaluation Parameters of Simvastatin Dry Syrups

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Color	**yellow**	**yellow**	**yellow**	**yellow**	**yellow**	**yellow**	**yellow**	**yellow**	**yellow**
Odor	**Strawberry**	**Strawberry**	**Strawberry**	**Strawberry**	**Strawberry**	**Strawberry**	**Strawberry**	**Strawberry**	**Strawberry**

Appearance	**Powder**	**Powder**	**Powder**	**Powder**	**Powder**	**Powder**	**Powder**	**Powder**	**Powder**
Bulk density (gm/cc)	**0.412 ±0.128**	**0.434 ±0.194**	**0.426 ±0.139**	**0.449 ±0.180**	**0.434 ±0.142**	**0.446 ±0.181**	**0.457 ±0.161**	**0.462 ±0.152**	**0.470 ±0.172**
Tapped density (gm/cc)	**0.524 ±0.182**	**0.572 ±0.175**	**0.535 ±0.162**	**0.539 ±0.168**	**0.529 ±0.177**	**0.545 ±0.175**	**0.563 ±0.185**	**0.571 ±0.191**	**0.568 ±0.153**
Angle of repose	**21.45 ±1.35**	**20.43 ±1.21**	**22.29 ±1.29**	**22.34 ±1.28**	**21.38 ±1.97**	**23.27 ±1.28**	**19.31 ±1.35**	**21.83 ±1.58**	**20.39 ±1.23**
Carr's index	**16.24 ± 1.69**	**15.86 ± 1.78**	**16.39 ± 1.64**	**15.86 ± 1.36**	**16.32 ± 1.21**	**15.28 ± 1.36**	**16.93 ± 1.39**	**15.34 ± 0.98**	**14.27 ± 1.28**
Hausner's ration	**1.21± 0.182**	**1.26± 0.153**	**1.32± 0.168**	**1.36± 0.189**	**1.32± 0.170**	**1.34± 0.170**	**1.30± 0.165**	**1.26± 0.192**	**1.39± 0.182**
Drug Content (%)	**98.14 ±1.74**	**99.25 ±2.08**	**97.34 ±1.48**	**99.37 ±1.28**	**98.67 ±1.71**	**99.74 ±1.87**	**99.89 ±1.45**	**98.97 ±1.26**	**98.97 ±1.26**
Viscosity (cps)	**451±9**	**678±6**	**874±5**	**428±6**	**597±7**	**865±5**	**674±4**	**867±7**	**1474±4**
Reconstitution Time (min)	**3.2**	**3.5**	**4**	**3.5**	**4.4**	**5.2**	**3.5**	**4**	**4.5**
pH	**6.5**	**6.3.**	**6.5**	**6.3**	**6.4**	**6.6**	**6.3**	**6.3**	**6.4**
Redispersibility (no. of strokes)	**13**	**12**	**11**	**14**	**12**	**10**	**12**	**11**	**8**
Sedimentation Volume Ratio	**0.51**	**0.71**	**0.81**	**0.49**	**0.64**	**0.8**	**0.71**	**0.81**	**0.95**

The values are presented as mean±SD (n = 3)

Redispersibility (no. of strokes):

To verify the reconstitutable suspension's physical stability, the sedimentation volume was measured. Values for the sedimentation volume can range from less than 1. The concentration of solid content determines the final height of the solid phase upon settling. For our purposes, a more extended amount of time is desired, although the sedimentation volume (F) should be at least 0.9 for one hour to achieve a satisfactory suspension.

Table 2 displays the sedimentation volume for the formulations above. According to the results, even after seven days, the sedimentation volume of formulation batch F9 was 0.95, which is much closer to the standard value of 1, indicating that there was no solid content sedimentation after the seven days. This resulted from the use of 3% CMC as a suspending agent, which holds the suspended solid particles in place. According to the findings, the ideal suspending agent concentration needed to produce a high-quality Simvastatin suspension was 3% CMC. Because batch F9 had a lower sedimentation than all other formulations, its formulation was superior to the others.

In-vitro Drug Release Studies:

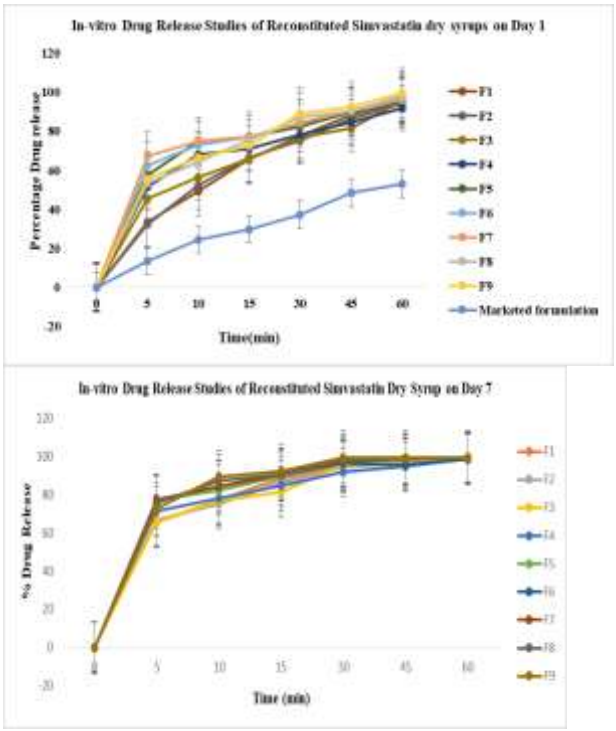

Figure 2: In-vitro drug release studies of Simvastatin dry syrups

Simvastatin dry syrups were reconstituted, and an in-vitro dissolution rate was measured using DISSO 2000, Lab India, on the first and seventh days. USP type II paddle stirrer operating at 50 rpm is part of an apparatus used in an 8-station dissolution rate test. A dissolving medium of 0.1 N HCl (900 ml) kept at 37±0.5ºC was utilized.

On day one, all reconstituted dry syrups released around 32.45%±1.21 to 55.45%±1.36 at 5min intervals, and after 60min, all the formulations released 91.85%±1.36 to 99.52%±1.58 amount of the drug and on day seven all the formulations released around 65-77% of the drug within 5min, and they released 99% of the drug over 6omin. The in-vitro drug release of dry syrups was compared with the drug release of the marketed formulation. Marketed formulation exhibited 13.45%±1.36 in 5min and 53.12%±1.36 of drug release over 60min. Simvastatin is available in solid dispersion form in dry syrup formulations. Due to that reason, SMV is dissolved in the reconstituted vehicle and is available for release; when the reconstituted dry syrup is added to the dissolution medium, it might release more drugs than a conventional tablet.

Release Kinetics

Drug release data from all of the simvastatin dry syrup formulations were tested for goodness of fit using linear regression analysis in accordance with first-order kinetics, zero-order kinetics, and drug release equations in vitro. Based on the above data and the regression coefficients obtained from the linear regression analysis, it is clear that the improved formulation (F9) adheres to first-order release kinetics.

Figure 3: Zero order release profile of formulation F9

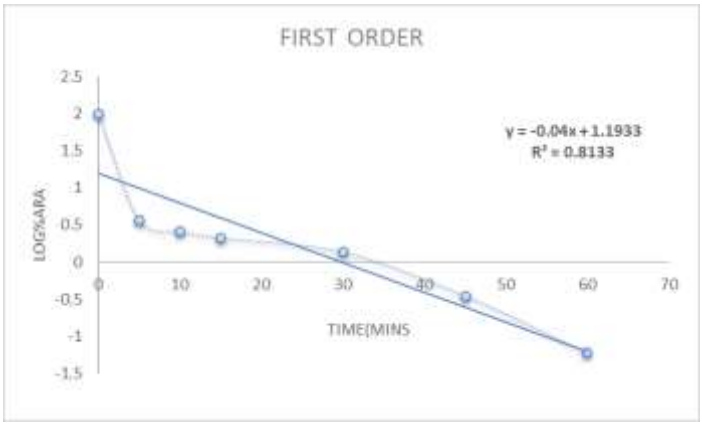

Figure 4: First order release profile of formulation F9

Table 3: Kinetic data of the formulation F9

ORDER OF KINETICS	ZERO-ORDER	FIRST ORDER
REGRESSION (R)	0.244	0.813

The drug release from the simvastatin dry syrup was explained by using mathematical model equations such as zero order, first order, and equation methods. Based on the regression values, it was concluded that the optimized formulation F9 follows First-order Kinetics.

Accelerated stability study

An investigation of stability was carried out on the refined recipe. For a duration of three months, the formulations were kept in a stability chamber at 40 ± 2°C and 75 ± 5% relative humidity, sealed inside an airtight container. After that, the samples were taken out at intervals of 30 and 90 days, and their drug content and in vitro dissolution investigations were assessed.

After three months the formulation did not change its colour and odour which indicates physically the formulation is stable. Drug content of the formulation was found to be 97.10±1.20 and the formulation reconstituted with water and tested for its pH and pH of the suspension showed that 6.3 indicating that the formulation is resistant to pH changes.

Reconstituted dry syrup was subjected for drug release studies and the percentage drug release was found to be 98.34±1.74over 60min.
There is no significant deviation in the test results has been observed after subjecting the formulation to accelerated stability studies. Which indicates that the formulation 9 (F9) is a stable formulation.

Table 4: Accelerated Stability testing of Optimized formulation (F9)

S.No	Sampling Interval	Parameters	Observations
1	Initial	Appearance	Yellow
		Drug Content	100.21±1.87
		pH	6.4
		% Drug release after 60min	99.94±1.26
2	One month	Appearance	Yellow
		Drug Content	98.54±1.62
		pH	6.4
		% Drug release after 60min	98.47±1.62
3	Three months	Appearance	Yellow
		Drug Content	97.10±1.20
		pH	6.3
		% Drug release after 60min	98.34±1.74

Particle size and Surface Characterization

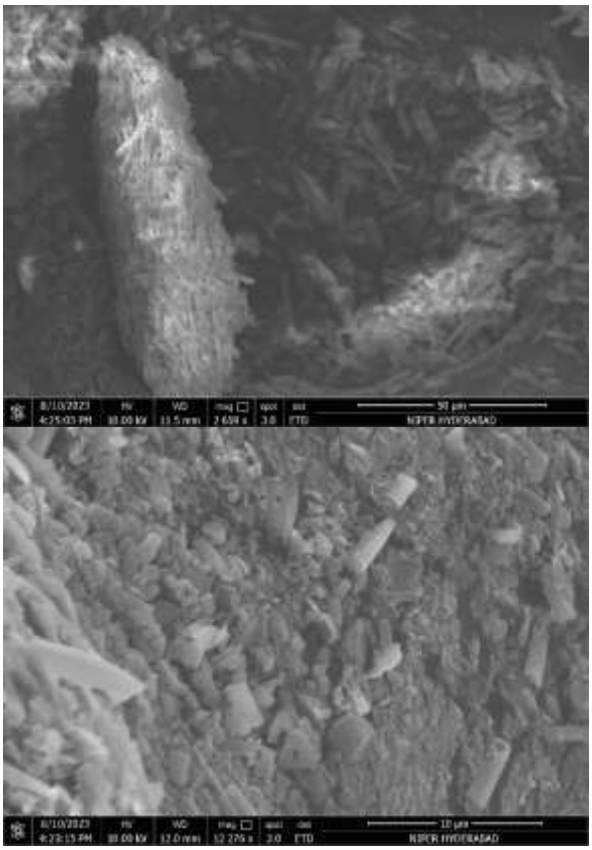

Figure 6: Scanning electron Microscopic view of Simvastatin dry syrup

Scanning electron micrographs of optimized dry syrup formulation have been shown in Figure 6. The particle size of the dry syrup powder is excellent particle size, and the surface of the particles is rough.

CONCLUSION:

Simvastatin pediatric dry syrups were developed using a solid dispersion technique. The formulations had acceptable color and odor, which are essential for patient compliance. All developed formulations exhibited good content uniformity and 99% drug release over a 60-minute time interval. Based on the results obtained from the tests after reconstitution of dry syrup, it is clear that the formulation containing carboxy methyl cellulose (CMC) in 2%W/W concentration exhibited better Viscosity, redispersibility, sedimentation volume than that of remaining formulations. So, formulation with 2% CMC, i.e., F9 selected as the optimized formulation. The optimized formulation was subjected to accelerated stability studies for three months. The accelerated stability studies also revealed that the formulation is stable. In-vitro drug release data was fit into goodness of fit, and the results showed that the drug release from the formulation exhibited first-order kinetics.

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CONFLICTS OF INTEREST:

Authors do not have any conflicts of interest.

REFERENCES:

1. Parmar Pratik, Dr. Patel M.R., Dr.Patel K.R., Dr.Patel N.M.; A Review On Taste Masking Pediatric Dry Syrup. International Journal Of Universal Pharmacy And Bio Sciences, 2013; 2(3): 552-568(ISSN): 2319-8141.
2. Bardeskar Casilda, And Geeverghese Rachel; Reconstitutable Oral Suspensions (Dry Syrups): An Overview. World Journal Of Pharmaceutical Research, Volume 4, Issue 3, 462- 484. ISSN 2277– 7105.
3. Ofner Cm, Sachnare Rl, And Schwartz Jb; "Reconstitutable Oral Suspension"Corporation, Nj,1984; Pg.243-259.
4. Sharma Vijay, Chopra Himanshu; Role Of Taste And Taste Masking Of Bitter Drugs In Pharmaceutical Industries An Overview. International Journal Of Pharmacy And Pharmaceutical Sciences: Vol 2, Suppl 4, 2010; 0975-1491.
5. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G. Development of self-micro emulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of Simvastatin in beagle dogs. Int J Pharm. 2004 Apr 15;274(1-2):65-73. doi: 10.1016/j.ijpharm.2003.12.028, PMID 15072783.
6. McClelland GA, Stubbs RJ, Fix JA, Pogany SA, Zentner GM. Enhancement of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase inhibitor efficacy through administration of a controlled-porosity osmotic pump dosage form. Pharm Res. 1991 Jul;8(7):873-6. doi: 10.1023/a:1015899328105, PMID 1924137.
7. Cheng H, Sutton SC, Pipkin JD, Zentner GM, Rogers JD, Schwartz JI. Evaluation of sustained/controlled-release dosage forms of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase inhibitors in dogs and humans. Pharm Res. 1993;10(11):1683-7. doi: 10.1023/a:1018997308946, PMID 8290485.
8. Jyothi Nakka, V. N., Gubbiyappa, K. S., & Nagaraju, N. (2024). Enhancement Of Dissolution And Bioavailability Of Simvastatin By Solid Dispersion Technique Using Sugar-Based Carriers. International Journal Of Applied Pharmaceutics, 16(1), 239–245. Https://Doi.Org/10.22159/Ijap.2024v16i1.49442.
9. Shalini Sharma, S Lewis; Taste Masking Technologies A Review; Int J Pharm and Pharma Sci; 2010; 2(2); 6-13
10. Harwood RJ, Rowe RC, Sheskey P.J., and Weller PJ. In Handbook of Pharmaceutical Excipients; Pharma Press, London, UK; 2003; 6th Edn; 662.

11. JLM Bellido, M.N. Gutierrez Zufiaurre, F.J. Sanchez Hernandez, G.Yagüe Guirao, M. Segovia Hernandez, J.A. Garcıa-Rodrıguez; In vitro activity of linezolid, Synercid and telithromycin against genetically defined high level fluoroquinolone-resistant methicillin-resistant Staphylococcus aureus; Int J Antimicrob Agents; 2002; 20(1); 61-68
12. Richard G. Wunderink, Sue K. Cammarata, Thomas H. Oliphant, Marin H. Kollef; The Linezolid Nosocomial Pneumonia Study Group; Methodist Healthcare Memphis; 2003; 980-988.
13. S.B. Sateesha, A.J.Rajamma, H.S.Shekar, R.K Mahammad Mutaar, A.Jayanthi, 'Formulation and stability study of palatable norfloxacin dry syrup: comparision among different preparation methods, Asian Journal of Pharmaceutical Sciences, 2010;5(5):175-184.
14. Martin Alfred, "Physical Pharmacy," Edn.6th, B.I. Warely Pvt. Ltd. New Delhi, 1994; 413-414.
15. Lories I. Bebawy; Stability-indicating methods for determining linezolid in the presence of its alkaline-induced degradation products; Talanta; 2003; 60(5); 945-953.
16. Vikas Sapre et al., formulation and evaluation of dry syrup, 05/issue:06/June-2023.
17. Chime Salome Amarachi et al., Kinetics and mechanisms of drug release from swellable and nonswellable matrices: A review, 4(2):97-103,2013.
18. Kulkarni M, Vishwakarma B, Sen S, Anupuram S, Date AA. Development and evaluation of taste-masked dry syrup formulation of potassium chloride. AAPS Open. 2019;5(1):1. doi: 10.1186/s41120-019-0030-z. Epub 2019 Jan 22. PMID: 30957011; PMCID: PMC6421559.