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PREPARATION AND CHARACTERISATION OF SOLID DISPERSION OF SIMVASTATIN BY EMPLOYING STARCH CITRATE AS A CARRIER

V G Gayathri*, K. Charitha, K. Dev Kumar, B. Jayasree, S. Sai Charan, D. Susmitha, A.G. Vedha Kamakshi, M. Niranjan babu

Department of Pharmaceutics, Seven Hills College of Pharmacy, Venkataramapuraam, Tirupati-517561, A.P

*Corresponding author E-mail:**gaya3prabhu2018@gmail.com**

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ABSTRACT

Solid dispersion technique is successfully applied to improve the solubility and dissolution rate, there by bioavailability. There are several carriers available for enhancement of the solubility and dissolution rate such as polymers, superdisintegrants, cyclodextrins, carbohydrates, surfactants, hydrotropes, polyglycolized glycerides, acids and dendrimers. Even though various carriers are available for the improvement of dissolution rate of the drug, there is need of development of new carriers. The aim of the present study is to formulate, characterize and evaluate starch citrate as a carrier in solid dispersions for enhancing the dissolution rate of simvastatin. Simvastatin solid dispersions are prepared by employing starch citrate and poly ethylene glycol as carriers by two different methods, i.e., solvent evaporation, and kneading method. Solid dispersion with carrier Starch citrate and polyethylene glycol was prepared in different drug: carrier ratios like; 1:1, 1:2, 1:3. The efficacy of starch citrate as a carrier is compared with the poly ethylene glycol. Results of FTIR were revealed that there were no interaction between drug, starch citrate and other excipients. All the solid dispersion formulation were evaluated for flow properties viz. Angle of repose, Bulk density, tapped density, Carr's compressibility index, and Hausner's ratio. Dissolution of the Simvastatin increased with increasing proportions of carrier in both the methods. Among all the formulations the invitro release prepared by kneading method shows high release than solvent evaporation method.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion [1, 2]. Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route [3, 4]. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption [5]. The enhancement of oral

bioavailability of poorly water soluble drugs becomes one of the most challenging aspects of drug development. Simvastatin is a methyl analogue of lovastatin and acts as an HMG-CoA reductase inhibitor effective in the treatment of hypercholesterolaemia [6]. Simvastatin, a widely used antihyperlipidemic HMG Co-A reductase inhibitor drug which belong to the Class II under BCSand exhibit low and variable oral bioavailability [7]. The most commonly used techniques to increase dissolution rate are particle size reduction, salt formation and lyophilization, but all these methods have practical limitations like improper enhancement of solubility and all the drugs are not suitable for these techniques. To overcome all these, solid dispersion technique is successfully applied to improve the solubility and dissolution rate, there by bioavailability [8].Solubility enhancement can be achieved by increasing the surface area of the drug which is accessible to the dissolution medium. Molecular dispersion of the drug in carriers may lead to particle size reduction and surface area enhancement, which results in improved dissolution rates [9]. There are several carriers available for enhancement of the solubility and dissolution rate such as polymers, superdisintegrants, cyclodextrins, carbohydrates, surfactants etc. Even though various carriers are available for the improvement of dissolution rate of the drug, there is need of development of new carriers. One such attempt was made to prepare chemically modified starch citrate which acts as a promising carrier in the formulations of solid dispersion. Native starches are undesirable for many applications, because of their inability to withstand processing conditions such as extreme temperature, diverse pH, high shear rate, and freeze thaw variation. To overcome this, modifications are usually done to enhance or repress the inherent property of native starches and to impact new properties to meet the requirements for specific applications. The modifications alter the properties of starch,including solution viscosity, association behaviour, and shelf life stability in final products. Modified starches were established as multifunctional excipient in the pharmaceutical and food industry. The swelling property of the starch citrate in water was compared with native starch and it was found that the % swelling index of native starch was less than the modified starch. Since increase in swelling power of a starch can used as a carrier in the pharmaceutical industry, so modified starch citrate might be used as carrier in solid dispersion formulations [10]. The aim of the present study is to formulate, characterize and evaluate starch citrate as a carrier in solid dispersions for enhancing the dissolution rate of simvastatin. And the efficacy of starch citrate is compared with Poly ethylene glycol.

2. MATERIALS AND METHODS:

2.1 Materials:

Drugs and chemicals: Simvastatin was obtained from Apex Laboratories, Chennai, as a gift sample. Other chemicals used where Citric acid (SDFCL-SD Fine Chemicals), Sodium hydroxide (SDFCL-SD Fine Chemicals), Potato starch (Final chemicals Ltd, Ahmadabad), poly ethylene glycol 6000 (sigma Aldrich), methanol (neutron water tech).

2.2 METHODS

Procedure for preparation of Starch Citrate: Starch citrate was prepared based on the method of modifications with citric acid as follows. Citric acid (20g) was dissolved in 20 ml of water and its pH was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made upto 50 ml by adding water. The citric acid solution (50 ml) was mixed with 50g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (280C). The tray was then placed in forced air oven and dried at 60^0C for 6 h. The mixture obtained was ground and further dried in a forced air oven at 130^0C for 2 h. The dry mixture was repeatedly washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50^0C to remove the water/moisture completely. The product obtained was ground and sized. Citric acid forms reactive anhydride upon heating by loosing water molecule .The reactive anhydride can react with starch to firm starch citrate. Figure no 1 Shows the reaction involved in the preparation of starch citrate [11].

Table no 1: Formulation design

S.no	Method	Formulation code	carrier	Drug : Polymer ratio
1	Solvent evaporation	F1	Starch citrate	1:1
2		F2	Starch citrate	1:2
3		F3	Starch citrate	1:3
4	Kneading method	F4	Starch citrate	1:1
5		F5	Starch citrate	1:2
6		F6	Starch citrate	1:3
7	Solvent evaporation	F7	PEG	1:1
8		F8	PEG	1:2
9		F9	PEG	1:3
10	Kneading method	F10	PEG	1:1
11		F11	PEG	1:2
12		F12	PEG	1:3

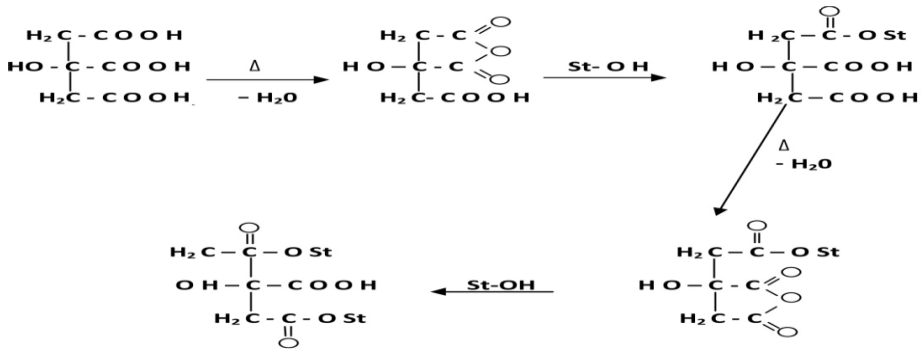

Figure no 1: **Starch citric acid reaction.**

Table no: 2 Physiochemical characterizations of starch citrate and starch

S.No.	Property	Result
1.	Solubility	Insoluble in all aqueous and organic solvents tested
2.	PH (1% w/v aqueous dispersion)	6.4
3.	Melting Point	Charred at 210^{o}C
4.	Viscosity (1% w/v aqueous dispersion)	1.87 cps
5.	Swelling Index	1400 %
6.	Gelling Property	No gelling and the swollen particles of starch phosphate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.
7.	Density	1.54g/cc
8.	Bulk Density	0.841 g/cc
9.	Angle of Repose	20.040
10.	Compressibility Index	16.29 %

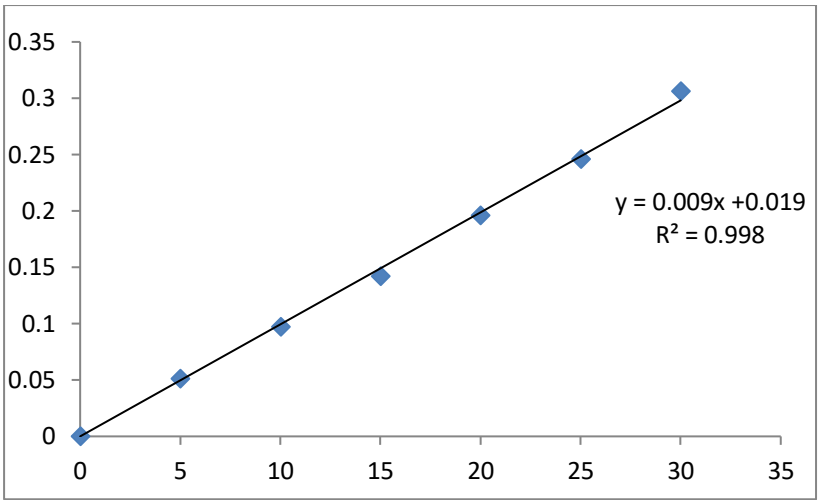

Figure no 2: **Calibration curve of Simvastatin.**

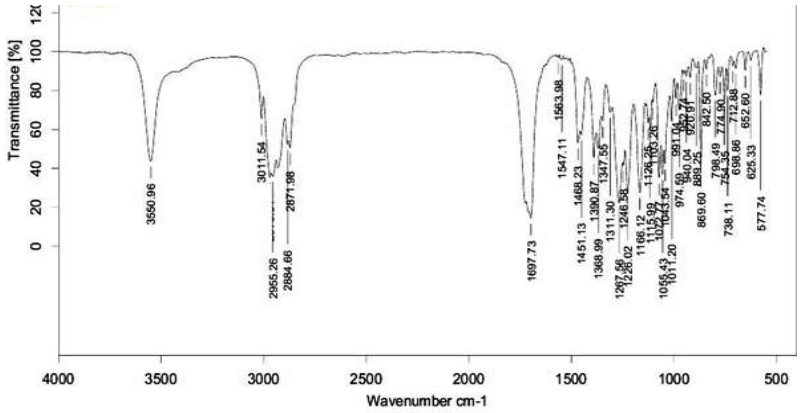

Figure no 3: FTIR spectrum of Pure drug simvastatin

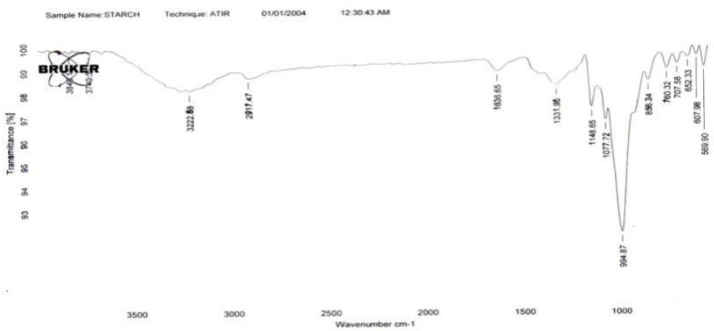

Figure no 4: FTIR spectrum of potato starch

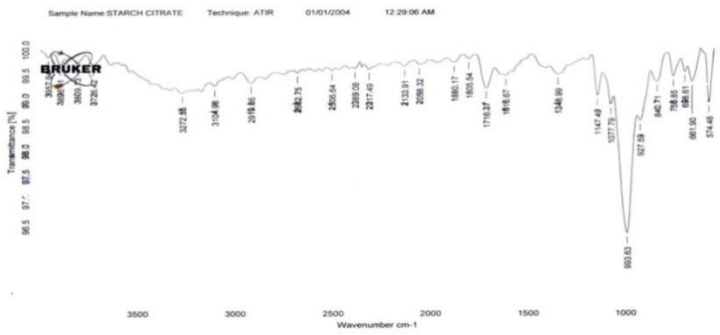

Figure no 5: FTIR spectrum of Starch citrate

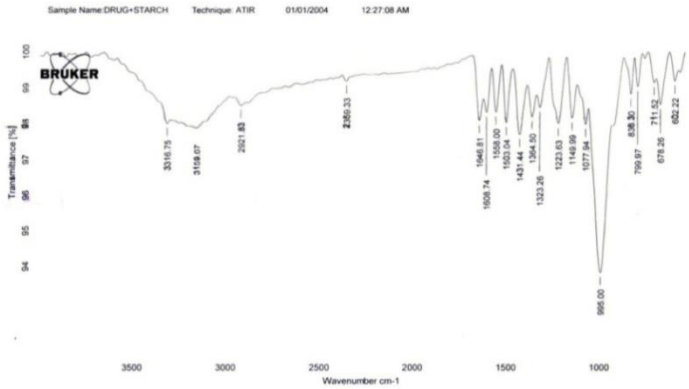

Figure no 6: FTIR spectrum of Drug + Starch citrate

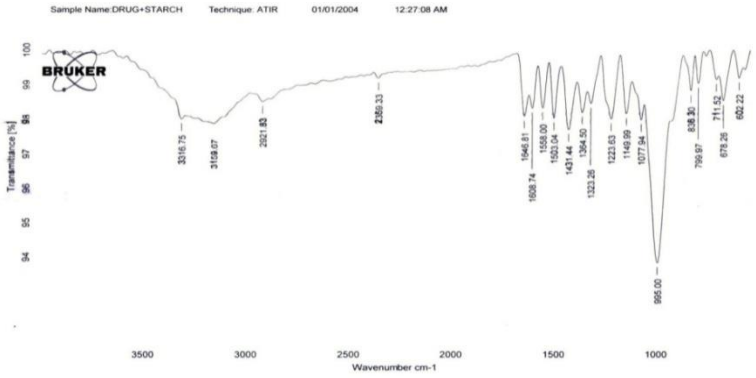

Figure no 7: FTIR spectrum of Drug + PEG

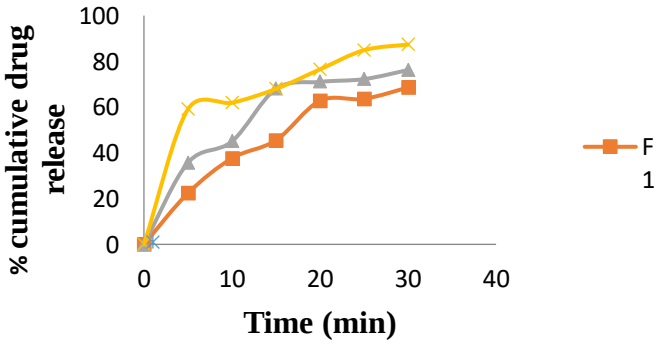

Figure no 8: *In vitro* Dissolution Profile of Solid Dispersion of Simvastatin in Phosphate Buffer pH 6.8 (F-1 to F-3)

Table no 3: Physical charecteristics of solid dispersion powder

Parameters	Bulk density (g/ml)±SD*	Tapped density (g/ml) ±SD*	Hausner's ratio ±SD*	Compressibility index (%)±SD*	Angle of repose (degrees) ±SD*
F_1	0.33±0.002	0.359±0.005	1.123±0.02	7.703±0.08	$24^{0}40^{1}$ ±0.39
F_2	0.292±0.002	0.322±0.0005	1.144±0.04	9.905±0.007	$25^{0}.52^{1}$±0.43
F_3	0.306±0.001	0.415±0.002	1.113±0.001	10.28±0.02	$27^{0}.14^{1}$±0.31
F_4	0.295±0.01	0.325±0.0015	1.165±0.005	10.07±0.005	$22^{0}.63^{1}$±0.004
F_5	0.30±0.012	0.357±0.03	1.197±0.09	13.85±0.01	$26^{0}.37^{1}$±0.28
F_6	0.40±0.04	0.475±0.001	1.165±0.005	14.31±0.0028	$26^{0}.43^{1}$±0.51
F_7	0.38±0.015	0.426±0.002	1.105±0.05	9.108±0.0026	$31^{0}.23^{1}$±0.22
F_8	0.36±0.013	0.415±0.005	1.145±0.005	12.55±0.05	$28^{0}.53^{1}$±0.28
F_9	0.306±0.012	0.357±0.03	1.165±0.005	13.85±0.005	$26^{0}.33^{1}$±0.39
f_{10}	0.395±0.015	0.435±0.05	1.197±0.09	9.84±0.01	$26^{0}.37^{1}$±0.43
f_{11}	0.3673±0.02	0.423±0.001	1.148±0.007	12.55±0.05	$26^{0}.42^{1}$±0.31
f_{12}	0.3873±0.0026	0.428±0.001	1.1040±0.002	16.13±0.076	$27^{0}.62^{1}$±0.004

Values are means of SD± n=3.

Table no 4: Drug content and percentage practical yield

Parameter	Drug content (%)	Percentage practical yield (%)
F_1	86.16±1.22	89.12±0.01
F_2	87.23±0.94	92.23±0.086
F_3	93.41±1.58	96.71±0.06
F_4	88.78±1.03	90.9±0.02
F_5	92.68±1.19	97.87±0.015
F_6	95.51±0.85	99.04±0.026
F_7	88.19±1.06	88.27±0.14
F_8	92.13±1.43	92.62±0.033
F_9	93.14±1.15	94.87±0.015
f_{10}	88.66±1.731.	93.65±0.17
f_{11}	91.45±0.05	91.57±0.49
f_{12}	93.45±0.06	93.86±0.04

Values are means of SD± n=3.

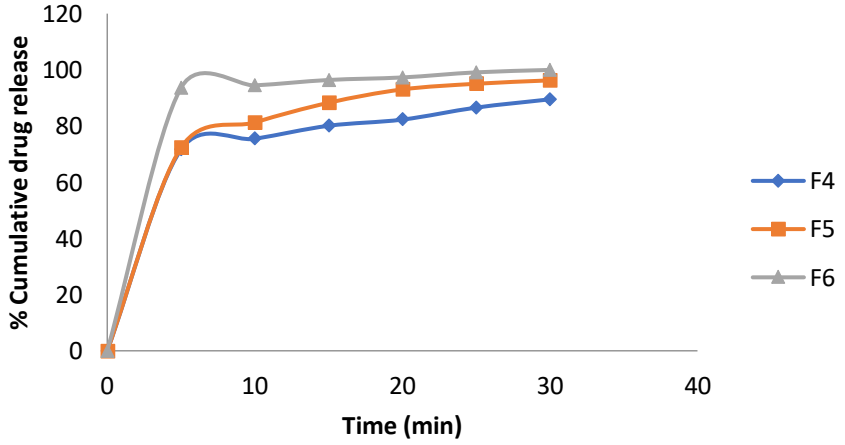

Figure no 9: *In vitro* Dissolution Profile of Solid Dispersion of Simvastatin in Phosphate Buffer pH 6.8 (F-4 to F-6)

In vitro drug release profile studies:

Table no 5: _Invitro_ drug release profiles of various tablet formulations

Formulation code	% Cumulative drug release						
	Time (min)						
	0	5	10	15	20	25	30
Pure Drug	0	19.49±0.31	24.46±0.40	32.565±0.28	37.52±0.4	46.56±0.06	49.64±0.1
F_1	0	22.38±0.45	37.62±0.49	45.51±0.32	62.77±0.23	63.60±0.29	68.61±0.13
F_2	0	35.65±0.67	45.00±0.62	67.98±0.18	71.03±0.95	72.24±0.65	76.22±0.98
F_3	0	59.07±0.84	61.89±0.57	67.96±0.56	76.50±1.0	84.89±0.35	87.32±0.69
F_4	0	71.60±0.59	75.44±0.39	80.08±0.1	82.28±0.31	86.55±0.44	89.50±0.48
F_5	0	72.25±0.41	81.26±0.34	88.27±0.28	93.02±0.41	95.04±0.21	96.24±0.21
F_6	0	93.56±0.73	94.46±0.86	96.38±0.64	97.29±0.30	99.10±0.02	99.96±0.37
F_7	0	49.86±0.74	54.74±0.44	66.77±0.50	69.11±0.40	71.28±0.10	72.41±0.211
F_8	0	52.07±0.84	63.89±0.57	68.96±0.56	76.50±1.0	84.89±0.35	86.32±0.69
F_9	0	57.76±0.67	58.59±0.56	76.80±0.32	84.42±0.38	87.71±0.30	91.98±0.16
F_{10}	0	69.07±0.84	74.89±0.57	81.96±0.56	83.50±1.0	84.89±0.35	87.32±0.69
F_{11}	0	72.85±0.96	81.43±0.28	86.88±0.49	95.41±0.49	92.36±0.07	93.23±0.93
F_{12}	0	85.24±0.54	91.20±0.51	93.72±0.27	96.00±0.17	97.40±0.45	98.42±0.23

Values are means of SD± n=3.

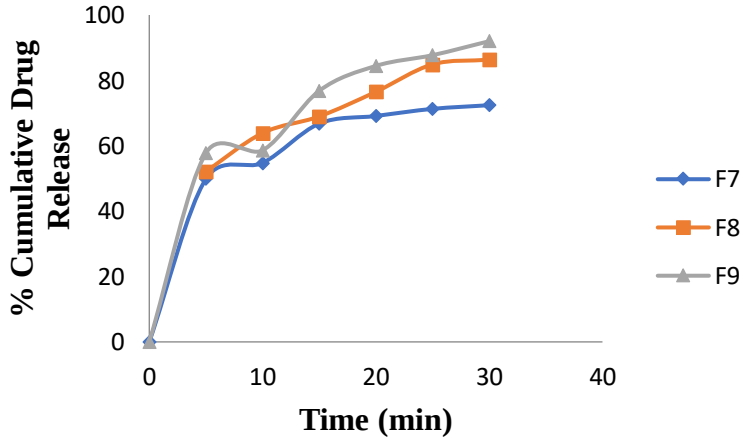

Figure no 10: _In vitro_ Dissolution Profile of Solid Dispersion of Simvastatin in Phosphate Buffer pH 6.8 (F-7 to F-9)

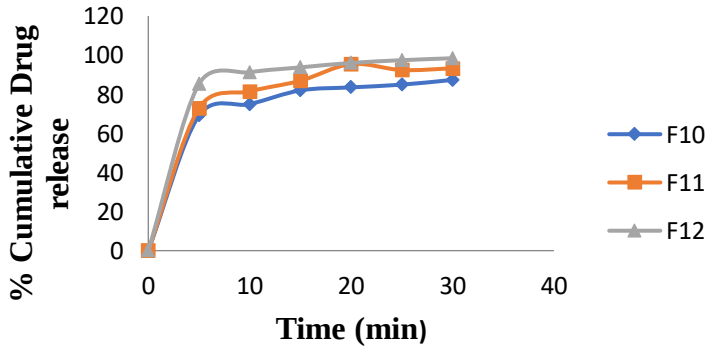

Figure no 11: _In vitro_ Dissolution Profile of Solid Dispersion of Simvastatin in Phosphate Buffer pH 6.8 (F-10 to F-12)

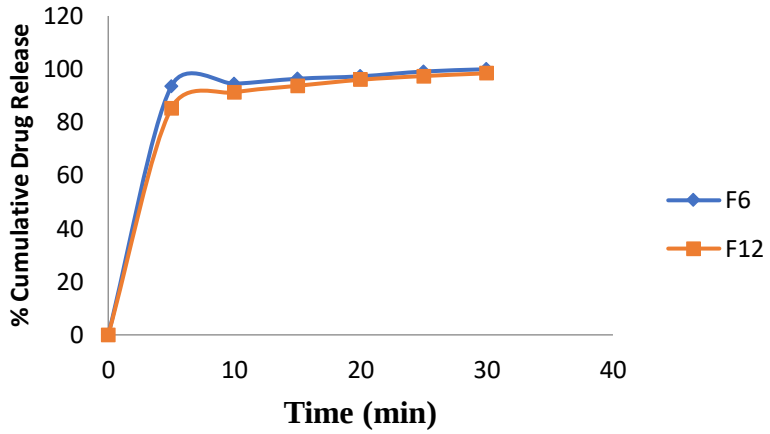

Figure no 12: Comparison of *In vitro* Dissolution Profile of Solid Dispersion of Simvastatin in Phosphate Buffer pH 6.8 (F-6and F-12)

Characterization of physiochemical properties of starch and starch citrate: The potato starch and starch citrate prepared were evaluated for following:

Solubility: Both starches solubility were tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether [12].

pH determination: The pH of starch and starch citrate was determined by using pen pH meter (Hanna instruments, Italy) [13].

Melting point: Melting point of both starches was determined by capillary method. Fine powders of sample were filled in glass capillary tube (previously sealed on one end) which is placed in melting point apparatus. The powders at what temperature it will melt were noticed [14].

Viscosity: Viscosity of 1%W/V dispersion of both starches (One gram of sample was dissolved in 100 ml of distilled water) in water was measured using Ostwald Viscometer[15].

Swelling index: 10 ml of water and light liquid paraffin was taken in two different graduated test tubes. The given sample (200 mg) was added to each test tube and mixed to form dispersion. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows [16].

$$S.I(\%) = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \text{ x } 100$$

Test for Gelling property: The gelling property (gelatinization) of the starch and starch citrate prepared was evaluated by heating a 7% w/v dispersion of each in water at 100ºC for 30 min [17].

Determination of flow property: Density (g/cc) was determined by liquid displacement method using benzene as liquid. Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Bulk density (D_B): The bulk density was expressed in terms of g/cc and calculated by formula [18].$D_B = W/ V_B$

Where, W is the weight of the powder, V_B is the bulk volume of the powder

Tapped Density (D_T): Tapped bulk density was measured by tapping the measuring cyllinder filled with the sample on a plane surface and record the tapped volume [19].

$$D_t = W/ V_T$$

Where, W is the weight of the powder, V_T is the Tapped volume of the powder

Angle of repose: Angle of repose was measured by fixed funnel method. It

determines flow property of the powder. The sample was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by following formula [20].

$\text{Tan } \theta = h / r$, $\theta = \text{Tan}^{-1} (h / r)$

Where, θ is the angle of repose, h is the height in cm; r is the radius in cm

Compressibility index: Compressibility index (CI) was determined by measuring the initial volume (Vo) and final volume (V) after hundred tappings of a sample of starch citrate in a measuring cylinder [21].

Compressibility index (CI) = (Vo – V/ Vo) X 100.

Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula [22].

$$\text{Hausner's ratio} = D_T/D_B$$

Where, D_T is the tapped density, D_B is the bulk density

FTIR: I.R spectroscopy can be used to investigate and predict any physiochemical interaction between selected excipients and simvastatin. 10mg of the sample and 400mg of KBr were taken in a mortar and triturated. A small quantity of triturated sample was taken into a pellet maker and compressed at 10 kg/cm^2 using a hydraulic press. The pellets was kept onto the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in Burker Spectrophotometer. Samples were prepared for Potato starch, Pure drug (Simvastatin), Starch citrate, physical mixture of drug and PEG, drug and starch cirate. The spectra obtained through those samples were compared and interpreted for the shifting of functional peaks and disappearance or appearance of new functional peaks [18].

Development of calibration curve of simvastatin in Phosphate Buffer pH 6.8: The beers-lamberts range of simvastatin was reported to be 5-30µ/ml. Calibration curve was developed using phosphate buffer pH 6.8. Serial dilutions of 5 to 30 µg/ml were prepared and the absorbance values of these solutions were measured against the reagent blank at 247 nm using UV visible spectrophotometer. Calibration curve was plotted for absorbance Vs concentration [18].

Preparation of solid dispersion: Simvastatin solid dispersions are prepared by employing starch citrate and poly ethylene glycol as a carrier by two different methods, i.e., solvent evaporation, and kneading method in different ratios. Solid dispersion with carrier Starch citrate and polyethylene glycol was prepared in different drug: carrier ratios like; 1:1, 1:2, 1:3. The efficacy of starch citrate as a carrier is compared with the poly ethylene glycol. Totally 12 formulations were prepared by changing the ratios of the carriers and as shown in Table no .1

Solvent evaporation: Drug and carrier were taken in a ratio of 1:1, 1:2, and 1:3. The drug was dissolved in methanol to get a clear solution in a china dish. The starch citrate was then added to clear drug solution and dispersed. By heating, at 50°C on a heating mantel, the solvent was removed and sieved (#100) and kept in a desiccator [19].

Kneading method: Drug and carrier were mixed geometrically to which methanol added. The mixture was stirred to form thick slurry and further kneaded to facilitate evaporation of methanol. The resultant product was dried (at 55°C), pulverized, sieved and stored in a desiccator until further use [19, 20].

Flow properties of solid dispersion: Flow properties of the powdered blend was evaluated for flow properties viz. Angle of repose, Bulk density, tapped density, Carr's compressibility index, and Hausner's ratio.

Determination of percent yield: The percent yield of simvastatin solid dispersions can be determined by using the following expression[19].Percent yield= (weight of prepared solid dispersion / weight of drug + carriers) × 100

Determination of percent drug content: Solid dispersions equivalent to 20 mg of simvastatin were separately taken and added to 100 ml of phosphate buffer 6.8 in stopper

conical flask. The sealed flasks were agitated on a sonicator[19]. The solution was diluted with phosphate buffer 6.8 and was assayed by a UV VIS spectrophotometer for drug content at 247 nm using the following expression:

% drug content = (Actual amount of drug in solid dispersions / Theoretical amount of drug in solid dispersion) × 100

***In vitro* drug dissolution studies:**The *In vitro*dissolution studies of the prepared solid dispersions was studied using dissolution test apparatus USP II employing a paddle stirrer at 50 rpm & at 37°± 0.5°C. Phosphate buffer of pH 6.8 (900ml) was used as a dissolution fluid. The samples equivalent to 40 mg, were subjected to dissolution. At time intervals of 10, 20, 30, 40, 50, 60 min samples (5ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45µm membrane filter, and suitably diluted and spectrophotometrically analyzed for drug content at 247nm wavelengths using a UV-VIS spectrophotometer[18].

RESULTS AND DISCUSSION: Starch citrate was prepared by reacting starch with citric acid at high and elevated temperatures. When citric acid is heated, it will dehydrate to yield an anhydride. The citric anhydride can thus react with starch to from starch citrate.

Characterization of physicochemical properties of starch and starch citrate: Modified starch citrate was found to be off white, crystalline, non- hygroscopic powder where as native potato starch was white, non-crystalline. All the physiochemical charecteristics were evaluated and the results are given in the table no 2. For native starch, angle of repose was $32^0.24^1$ exhibiting good flow property and for modified starch, the angle of repose was $20^0.04^1$, exhibiting excellent flow property. For native starch, compressibility index (%) was 21.14%, flow is passable and for modified starch, it was 16.29%, fair powder flow. For native starch and modified starch hausner's ratio were found be 1.12 and 0.10 respectively exhibiting excellent flow property.

Calibration curve of Simvastatin: Calibration of the drug was done to found out the linearity between concentration of drug in the solution and its optical density. It was concluded that the perfect linearity between the concentration and absorbance was present within the concentration ranging from 5.0µg/ml to 30.0µg/ml. Figure no 2 shows the calibration of simvastatin using phosphate buffer pH 6.8.

Compatability studies: An I.R study was carried out to check the compatibility between the selected excipients and simvastatin. The spectra obtained for IR Studies at wave length from $4000cm^{-1}$ to $400cm^{-1}$ were shown in the figure 3-7. After interpretation through the above ,spectra it was confirmed that there are no major shifting as well as no loss of functional peaks between the spectra of drug, starch citrate, starch, physical mixture of drug + starch citrate, and physical mixture of drug + PEG. From the I.R studies it was concluded that, the excipients are compatible with the selected drug simvastatin.

Evaluation of solid dispersion:

Physical Characteristics of Solid Dispersion Powder: Physical characteristics of all solid dispersion powders were examined for angle of repose, bulk density, tapped density, carr's index (CI), Hausner's ratio and values for which are reported in the table no: 3. From the values of bulk and tapped density the values of carr's index and Hausner's ratio were calculated. And the flow properties of granules were found to fall within the official USP limits.The results of Percent practical yield for all formulations of solid dispersions found to be 89 to 99%. Maximum yield was found to be 99.04 % for the formulation F_6. The drug content of the prepared SDs was found to be in the range of 86.16% to 95.5 % respectively as per official limits. Maximum % drug content was found in the formulation F6. The drug content and practical percentage yield of all the formulations were given in the table no: 4. Cumulative amount % of drug release for various formulations were given in table no: 5. And the invitro drug release graph profile for were given in figure no: 8 - 12. Dissolution of the Simvastatin increased with increasing proportions of carrier in both the methods. The solid dispersions of simvastatin showed an increased rate of dissolution in comparison to pure drug. After comparing the dissolution profile of all formulations, it was found that the

dissolution rate increases to the maximum extent in kneading method containing starch citrate as a carrier in the ratio of 1:3 (Simvastatin: Starch citrate). Thus F6 formulation is considered as the best formulation. Among all the formulations the invitro release prepared by kneading method shows high release than solvent evapouration method. The efficacy of starch citrate as a carrier is due to swelling mechanism of starch citrate exhibited in solid dispersion. From the obtained results the modified starches exhibit similar carrier behaviour like polyethylene glycol. Hence starch citrate can considered as a novel carrier and solubility enhancer of poorly soluble drugs.

SUMMARY AND CONCLUSION

The modified starch citrate was prepared by reacting potato starch with citric acid at elevated temperatures. The efficacy of starch citrate as a carrier is due to swelling mechanism of starch citrate exhibited in solid dispersion. The efficacy of starch citrate as a carrier is compared with the poly ethylene glycol. Among all the formulations the invitro release prepared by kneading method shows high release than solvent evaporation method. Dissolution of the simvastatin increased with increasing proportions of carrier in both the methods. Hence starch citrate can considered as a novel carrier and solubility enhancer of poorly soluble drugs and it can be concluded as a economical and better choice for commercial use.

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