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Preparation and characterization of solid dispersion tablet of simvastatin employing starch phosphate as carrier

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ABSTRACT

In this research we have prepared, characterized and evaluated the starch phosphate solid dispersion for increasing the dissolution rate of simvastatin. Solid dispersion of simvastatin in starch phosphate was formulated by solvent evaporation technique. In this research different batches were prepared by using the different concentration of the starch phosphate with other inactive ingredients. Dissolution study was performed for the evaluation of in-vitro, solid dispersion which releases the simvastatin faster and was compressed into tablet. Simvastatin solid dispersion was prepared by wet granulation and converted into tablet form. This solid dispersion gives the faster dissolution rate of 87.34% to 103.34% at 25- 30 minutes when it was compared with the conventional tablet.

Keywords: Simvastatin, Starch phosphate, FTIR spectroscopy, Solid dispersion, *In vitro* dissolution.

1. INTRODUCTION

Simvastatin (Figure 1) is a methyl analogue of lovastatin and acts as an HMG-CoA reductase inhibitor effective in the treatment of hypercholesterolaemia. Simvastatin, a widely used antihyperlipidemic HMG Co-A reductase inhibitor [1], drug which belong to the Class II under BCS [2] and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its absorption and dissolution rate is low and it requires enhancer to increase its dissolution rate and solubility. Several techniques such as micronization, cyclodextrin-complexation, and several material like, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, salts, prodrugs, micro emulsions and self emulsifying micro and nano disperse systems have been used to increase the dissolution rate, solubility and bioavailability of poorly soluble drugs. Among these approaches, solid dispersions in water dispersible excipients are a simple, industrially useful approach for increasing the solubility, dissolution rate and bioavailability of poorly soluble drugs [3]. Starch phosphate is one of the modified Starches used in the frozen food industry. It is produced by phosphorification of free hydroxyl Groups of anhydrous glucose units of starch molecule. These starch molecules are esterified with phosphate reagents. Starch Phosphate was reported as good disintegrant in different tablet formulations [4].The aim of the present research was to formulated, characterize and evaluate starch phosphate as a carrier in solid dispersions for enhancing the dissolution rate of simvastatin.

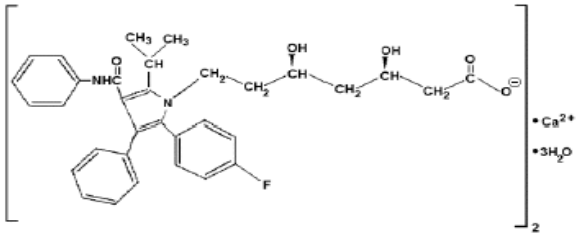

Figure - 1: Simvastatin structure.

2. MATERIALS AND METHODS

2.1. Materials

Simvastatin was obtained from A&A Pharma, Starch Phosphate was prepared in the laboratory, Methanol, Starch, Lactose, Magnesium sterate, PVP-K30were also obtained A&A pharma.

2.2. Preparation of starch phosphate

Starch phosphate was prepared in the industrial lab. Potato starch (200 g) and di-sodium hydrogen orthophosphate anhydrous (60 g) were suspended in 200 ml of distilled water and continuously stirred for 30 min. This wet Starch slurry was conditioned for 12 hr at room temperature (25℃). To enhance the

phosphorylation, then this mixture was heated in a forced air oven at 130℃ for 3 hr. The product obtained was ground and sized [5].

2.3. Characterization of starch phosphate

The starch phosphate prepared was characterized and evaluated for following.

2.3.1. Solubility

Solubility of the starch phosphate was tested indifferent media like water, aqueous buffers of pH 1.2, 4.6, and 7.5 and organic solvents such as ethanol, methanol, acetone, chloroform and petroleum ether [5].

2.3.2. pH

The pH of 1% w/v paste was measured by ph meter [5].

2.3.3. Melting point

The melting point of blend was determined using melting point apparatus [6].

2.3.4. Viscosity

Viscosity of 1% dispersion in water was measured using Viscometer [6].

2.3.5. Swelling index (SI)

Starch phosphate (250 mg) was added to 15 ml of water and white liquid paraffin taken in two different graduated cylinder and mixed. The dispersion in the cylinder was allowed to stand for about 12 hr. The volumes of the sediment of material in the glass cylinder were observed. The swelling index of the material was calculated as follows [7].

Volume of sediment in water – Volume of sediment in light liquid paraffin / Volume of sediment in light liquid paraffin X 100

2.3.6. Test for gelling property

The gelling property (gelatinization) of the starch and starch phosphate prepared was evaluated by heating 7% w/v of each in water at 100°C for 30 min [7].

2.3.7. Moisture absorption

Starch phosphate is hygroscopic in nature and it was evaluated by moisture absorption studies in closed desiccators at about 70% relative humidity and room temperature [7].

2.3.8. Particle size

Particle size analysis of granules was done by sieving using standard sieves [8].

2.3.9. Density

Density of material was determined by liquid displacement method using benzene as liquid [8].

2.3.10. Bulk density

Bulk density was determined by tap method in a graduated glass cylinder [8].

2.3.11. Angle of repose

Angle of repose was measured by fixed funnel method.[8]

2.3.12. Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (Vo) and final volume (V) after tappings of a sample of starch phosphate in a glass cylinder. Compressibility index was calculated using equation [8]

Compressibility index (CI) = $V_0 - V / V_0 \times 100$

2.4. Preparation of solid dispersions (sd) of simvastatin in starch

Phosphate Solid dispersions of simvastatin Phosphate Solid dispersions of simvastatin and starch phosphate were prepared in different ratios of drug: carrier by solvent evaporation method. Simvastatin (2 g) was dissolved in Methanol (20 ml) to get a clear solution. Starch phosphate (2 g) was then added and dissolved. It was triturated for 10 min till complete evaporation of Methanol and then dried at 55℃. The dried mass was pulverized and sieved through mesh no. 100 [8,9].

2.5. Estimation of simvastatin in dissolution

An UV spectrophotometric method based on the measurement of absorbance at 238nm in Phosphate buffer pH 7.4 used for estimation of simvastatin [10].

2.6. Preparation of -SD tablets [11]

- Take lactose and starch phosphate add into the mixture.
- Add simvastatin slowly in the mixture during continuous mixing.
- Prepare P.V.P k 30 solution by dissolving in Q.S I.P.A.
- Add P.V.P k 30 solution in mixture with continuous mixing.
- When wet mass is obtained stop mixing and pass the mixed material through wet granulator and collect in to SS trays of tray dryer.
- Dry wet granulate in tray dryer below 40℃.
- After drying crush the granules with granulator.
- Add the granules in con mixer along with lubricant and disintegrant.
- Mixed the granules for 15 minutes and start compression by using punch size

9mm flat punch and then prepared tablets were evaluated for different tests.

2.7. Dissolution rate study

Dissolution rate of simvastatin tablets prepared was studied in phosphate buffer pH 7.4 (900 ml) employing USP Dissolution Rate Test Apparatus (pharmatest dissolution apparatus) with a paddle stirrer at 50 rpm. Simvastatin or its solid dispersions equivalent of 10 mg of simvastatin and a tablet containing 10 mg of simvastatin was used in each test. A temperature 37±1℃ was maintained in each test. Samples of dissolution medium (10 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for simvastatin at 238 nm. All the dissolution experiments were conducted in triplicate (n=3) [12,13].

3. RESULTS AND DISCUSSION

Starch phosphate was prepared by reacting starch with di-sodium hydrogen phosphate at elevated temperatures. Prepared Starch phosphate was found to be white, crystalline, non-hygroscopic powder. The prepared starch phosphate was characterized by various physical properties. When tested for M.P., it charred at 135°C. Prepared Starch phosphate was poorly soluble in water, other aqueous fluids of acidic and alkaline pH and inorganic solvents tested. It exhibited good swelling (400%). In micromeritic evaluation, the angle of repose and compressibility index values revealed the excellent flow characteristic of prepared starch phosphate. The increase in dissolution rate of simvastatin was observed with solid dispersions .The feasibility of formulating simvastatin solid dispersions in starch phosphate into tablets retaining their rapid and higher dissolution rates was also investigated. The granules had good flow property. FTIR study showed there was no interaction between simvastatin and excipients**.** All the simvastatin tablets contain the simvastatin within the pharmacopoeial limits [14]. Hardness of the tablets was in the range 3 to 4.5 Kg/sq.cm. Percentage weight loss in the friability test was less than 0.320% in all the batches. Tablets formulated employing solid dispersions disintegrated rapidly within 1.33 min. Tablets formulated employing simvastatin pure drug disintegrated within 2.31 min. Simvastatin tablets formulated employing its solid dispersions in starch phosphate.

3.1. Preparation of standard stock solution

3.1.1. Standard simvastatin stock solution (100 µg/mL)

Simvastatin standard stock solution was prepared by weighing 10 mg of simvastatin and transferred to a 100 ml volumetric flask and volume was made up to100 ml with Methanol & Water in the ratio of 40:60(Methanol: Water) to get a concentration of 100µg/ml, The prepared solution is sonicated for 5 minutes and filtered through the whatman filter paper no. 41

Table - 1: Formulation of simvastatin trial

Name Of Materials	Units	Quantity
Simvastatin	mg	10.00
Lactose	mg	110-150
Starch phosphate	mg	50-100
Mg.Stearate	mg	0.5
IPA	mL	15.0

3.2. Calibration curve

A calibration curve was plotted over a concentration range of 3-18 µg/mL simvastatin. Accurately measured standard stock solution of simvastatin (0.3, 0.6, 0.9, 1.2, 1.5 &1.8mL) were transferred to a separate series of 10 mL of volumetric flasks and diluted to the mark with methanol and water in the proportion of 40:60. The absorbance of each solution was measured at the wavelengths 238.2 nm. Calibration curves (Figure 2) were constructed for simvastatin by plotting absorbance versus concentrations at wavelength. Reading was average of five determinations.

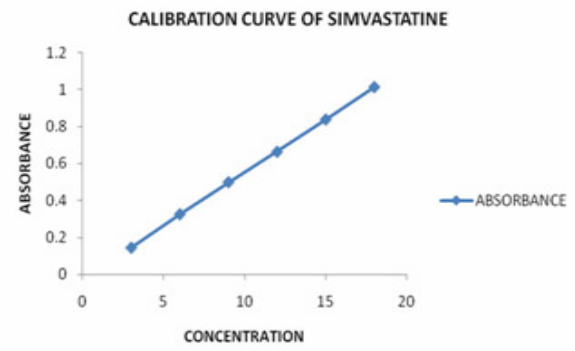

Figure - 2: Calibration curve

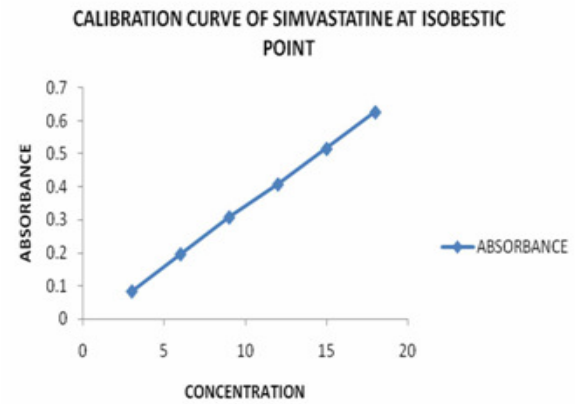

Figure - 3: Calibration curve

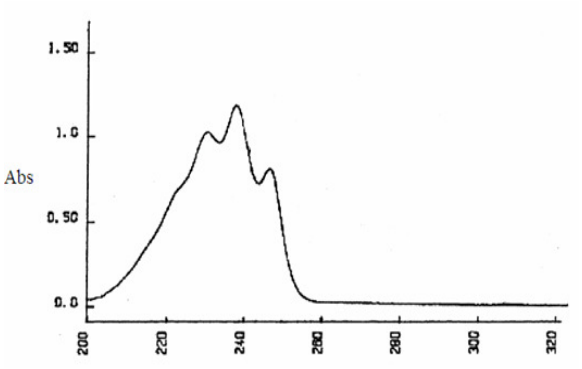

Figure - 4: UV Absorption Spectra of simvastatin.

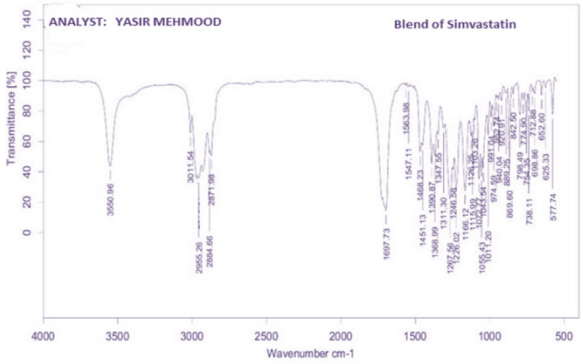

Figure - 5: FT-IR compatibility study of simvastatin blend.

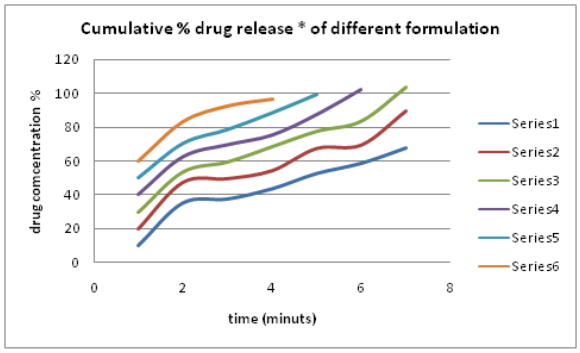

Figure - 6: Drug release graph.

Table - 2: Formulation using different concentration of SP

Formulation	API (mg)	Lactose (mg)	Starch phosphate (mg)	Mg sterate (mg)	PVP k 30 (mg)	IPA (ml)
S1	10	150	50	0.5	10	15
S2	10	140	60	0.5	10	15
S3	10	130	70	0.5	10	15
S4	10	120	80	0.5	10	15
S5	10	110	90	0.5	10	15
S6	10	100	100	0.5	10	15

Table - 3: Dissolution results of simvastatin

Time	Cumulative % drug release *					
	S1	S2	S3	S4	S5	S6
10	35.1	37.4	43.4	52.4	58.4	67.4
20	47.4	49.6	54.3	67.4	69.4	89.4
30	53.6	59.5	68.5	77.5	83.5	103.4
40	62.4	69.6	75.3	87.5	102.4	
50	70.3	78.5	88.4	99.3		
60	83.2	92.4	96.4			

Table - 4: Drug content of simvastatin in formulation.

Formulation	Drug (%)
S1	98.4
S2	99.3
S3	103.4
S4	99.4
S5	102.4
S6	103.3

Table - 5: Precompression study of granules.

Formulation	Bulk density g/cm3	Tappe density g/cm3	Compressibility (%)	Hausner ratio	Angle of response (degree)
S1	0.354	0.558	16.69	1.57	34.51
S2	0.345	0.558	17.32	1.57	32.12
S3	0.356	0.453	16.34	1.27	32.42
S4	0.376	0.556	15.32	1.47	32.23
S5	0.372	0.445	16.34	1.19	31.45
S6	0.345	0.521	17.34	1.51	30.23

Table - 6 : Post compression study of prepared tablets of simvastatin

Formulation	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)	Weight (mg)*	Disintegration (min)*
S1	3.4	0.34	98.4	220	2.3
S2	4.3	0.25	99.3	222	1.4
S3	3.2	0.15	103.4	224	1.0
S4	4.1	0.32	99.4	220	2.1
S5	4.3	0.38	102.4	217	1.4
S6	3.5	0.27	103.3	225	1.3

4. CONCLUSION

All the solid dispersions formulations gave rapid and higher dissolution of simvastatin. Starch phosphate prepared by reacting starch with di-sodium hydrogen phosphate at elevated temperatures and it was insoluble in water and give good swelling property without pasting when heated in water. Dissolution followed first order kinetics and increase in the dissolution rate of simvastatin. The Dissolution was also increased when the drug: carrier ratio was increased. simvastatin tablets formulated with solid dispersions in starch phosphate gave rapid and higher dissolution rate when compared to plain. These solid dispersions could be formulated into compressed tablets retaining their fast dissolution characteristics and complies official standards.

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