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Research Article

Formulation and evaluation of fast dissolving tablets of simvastatin using novel co-processed superdisintegrants

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Abstract: The aim of the present investigation was to develop fast dissolving tablets of Simvastatin, an lipid-lowering drug used for the reduction of VLDL. Due to its low solubility and its short biological half-life of 3 hours, fast dissolving tablets of Simvastatin were prepared using superdisintegrants in order to improve the dissolution rate, thereby the absorption. The influence of concentration of the Ac-Di-Sol was studied by a set of four formulations (F1, F2, F3, F4) with concentrations of Ac-Di-Sol viz, 2%, 3%, 4% & 5%w/w respectively. Also the influence of various superdisintegrants was studied by a set of three formulations (F4, F5 and F6) with three superdisintegrants viz, Ac-Di-Sol (5%), Croscarmellose sodium(5%), Crospovidone (5%) respectively. The formulation prepared with 5%w/w of Ac-Di-Sol was offered relatively rapid release of Simvastatin n when compared with other concentrations of Ac-Di-Sol. The formulation prepared with Crospovidone was offered relatively rapid release of Simvastatin when compared with other superdisintegrants. Various formulations were prepared incorporating a combination of superdisintegrants (Physical Mixtures and Co-processed Mixtures), Ac-Di-Sol and Crospovidone by direct compression method. Formulation containing Co-processed mixtures had less disintegration time as compared to the Physical mixtures. So, we can conclude that nature , concentration of the superdisintegrant and type of combination of superdisintegrants (Physical mixing vs Co-processing) showed influence on the rate of dissolution. The dissolution rate was found to follow first order kinetics.
Keywords: Simvastatin, Crospovidone , Ac-Di-Sol , Fast disintegrating tablets, solvent evaporation method

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INTRODUCTION

Simvastatin is designated as 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro -4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester. Simvastatin is used in the present study and widely accepted for its excellent lipid-lowering agent (HMG-CoA reductase inhibitor), whose solubility is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods(Micronization, Complexation, Solid dispersion etc). Another prerequisite for the fast dissolution may be the disintegration time of tablets. Because faster disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug. Solid oral dosage forms, especially tablets, remain one of the most popular because of advantages like patient convenience, ease of storage and dispensing, dose accuracy and easy manufacturability.

Fast dissolving tablets are defined as ―A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue [1]. In case of conventional tablets, physical problems with swallowing (Dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric and psychiatric patients. Difficulties and resistance to tablet-taking are common in all patient groups. In recent years, fast dissolving tablets have been developed to overcome problems related to swallowing difficulties [2]. Fast Dissolve, Quick Dissolve, Rapid Melt, Quick Disintegrating, Mouth Dissolving, Orally Disintegrating, Oro Dispersible, Melt-in-Mouth etc. are terms that represent the same drug delivery systems. The orally disintegrating property of tablet is attributed to a quick ingress of water into the tablet matrix, which creates porous structure and result in rapid disintegration. When put on tongue, these tablets disintegrate instantaneously, releasing the drug which dissolves or disperses in saliva. The drugs may be absorbed from mouth, pharynx or esophagus as the saliva passes down into the stomach. Advantages of the Fast dissolving tablets include ease of swallowing without the aid of water, rapid onset of action, enhanced dissolution rate, increased gastric absorption, improved

oral bioavailability, minimized first pass metabolism and improved patient compliance [3,4].

MATERIALS AND METHODS

Simvastatin was obtained from Natco Pharma, Hyderabad, India. Sodium starch glycolate, crosspovidone, croscarmellose sodium, mannitol, micro crystalline cellulose, talc and magnesium stearate were purchased from SD fine Chemicals Ltd, Mumbai. All other materials used were of analytical grade.

Preparation of co-processed superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method [5-6]. A blend of Crospovidone and Ac-Di-Sol (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 60 mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 60 mesh sieve and stored in airtight container till further use.

Preparation of Simvastatin tablets

Tablets containing 80 mg of Simvastatin were prepared by direct compression method. Drug was passed through sieve no 100. Simvastatin along with other excipients were mixed in a mortar. The resulting blend was lubricated with magnesium stearate and compressed into tablets using the Cadmach single punch (round shaped, 7mm thick) machine.

Micromeritic Properties of the Blend [7]

Bulk density

Blend was weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated by using the following formula

$$\text{Bulk density} = \frac{Mass of the powder}{Bulk volume}$$

Tapped density

Blend was weighed, transferred to a measuring cylinder and subjected to 100 tapings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula

$$\text{Tapped density} = \frac{Mass of the powder}{Tapped volume}$$

Carr's index

Carr's index was calculated by using the following formula

$$\text{Carr's index} = \frac{Tapped density - Bulk density}{Tapped density} \times 100$$

Hausner's ratio

$$\text{Hausner's ratio} = \frac{Tapped density}{Bulk density}$$

Angle of repose

Required quantity of blend was taken and poured into a hollow cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. Then height and diameter of the heap formed were noted down. The angle of repose (θ) was calculated by the formula

$$\text{Angle of repose, } \theta = \text{Tan}^{-1}\frac{h}{r}$$

Evaluation of Simvastatin Tablets

Average weight [8]

Five tablets were selected and were weighed collectively and individually. From the collective weight, average weight was calculated.

Drug content [9]

Twenty tablets were powdered, and 80 mg equivalent weight of simvastatin in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 233 nm.

Disintegration Time [8]

The disintegration time was determined in distilled water at 37±0.50 C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).

Friability [9]

Roche friabilator was used to determine the friability. Pre weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\%\text{FRIABILITY} = \frac{INITIAL WEIGHT - FINAL WEIGHT}{INITIAL WEIGHT} \times 100$$

Hardness [10]

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure.

Wetting time and Water absorption ratio [11]

A piece of paper folded twice was kept in a Petri dish containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time. The same procedure without Rosaline dye powder was followed

for determining the water absorption ratio R was determined according to the following equation.

$R = [(Wa – Wb)/Wb]\times 100$

Where, Wb and Wa were the weights of the tablet before and after water absorption.

In vitro dispersion time [12]

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37+/- 0.5°C. Time required for complete dispersion of tablet was measured.

Fineness of dispersion [13]

This test is performed by placing two tablets in 100 ml of water and stirring it gently, till the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 µm without leaving a residue on the mesh.

Dissolution studies[14]

Dissolution studies for simvastatin fast dissolving tablets were performed in pH 6.8 phosphate buffer using USP TDT-08L dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles are allowed to rotate at speed of 50 rpm. The dissolution medium was maintained at a temperature of 37+0.5 OC and samples are withdrawn at an interval of every 5 min the volume of the withdrawn samples are replaced by fresh dissolution medium in order to kept the volume of the dissolution medium as constant. The withdrawn samples are filtered and absorbance was measured at absorption maxima of 238 nm using UV-visible spectrophotometer.

RESULTS AND DISCUSSIONS

The influence of concentration of the Ac-Di-Sol on the performance of Simvastatin, a set of four formulations (F_1, F_2, F_3, F_4) were prepared using four different concentrations of Ac-Di-Sol (2%, 3%, 4% & 5%w/w) respectively. The formulated tablets were subjected to various quality control tests and the results were shown in Table 6. All the tablets complied with the Pharmacopoeial standards, but F_1 and F_2 failed to meet the fineness of dispersion requirements. The dissolution data was presented in Figure 2. The dissolution kinetics was presented in Table 8. The dissolution rate followed first-order kinetics (Figure 3) as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Simvastatin was found to be effected by the concentration of the superdisintegrant (Ac-Di-Sol) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the four formulations was F_4> F_3> F_2> F_1. The formulation prepared with 5%w/w of Ac-Di-Sol was offered relatively rapid release of Simvastatin when compared with other concentrations employed in this investigation.A statistically significant difference between dissolution efficiencies (DE_{25}) of Simvastatin tablets formulated with different concentrations of Ac-Di-Sol was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are presented in Table 9. The P value was found to be less than 0.05, which indicates that there was a significant difference between F_1, F_2, F_3, F_4 with respect to Dissolution Efficiencies (DE_{25}).

The influence of concentration of the Crospovidone on the performance of Simvastatin, a set of four formulations (F_5, F_6, F_7, F_8) were prepared using four different concentrations of Crospovidone (2%, 3%, 4% & 5%w/w) respectively. The formulated tablets were subjected to various quality control tests and the results were shown in Table 6. All the tablets complied with the pharmacopoeial standards, but F_9 failed to meet the fineness of dispersion requirements. The dissolution data was presented in Figure 5. The dissolution kinetics was presented in Table 11. The dissolution rate followed first-order kinetics (Figure 6) as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Simvastatin was found to be effected by the concentration of the superdisintegrant (Crospovidone) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the four formulations was F_{12}> F_{11}> F_{10}> F_9. The formulation prepared with 5%w/w of Crospovidone was offered relatively rapid release of Simvastatin when compared with other concentrations employed in this investigation. A statistically significant difference between dissolution efficiencies (DE_{15}) of Simvastatin tablets formulated with different concentrations of Crospovidone was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are presented in Table 12 . The P value was found to be less than 0.05, which indicates that there was a significant difference between F_5, F_6, F_7, F_8 with respect to dissolution efficiencies (DE_{15}).

The influence of physical mixture of superdisintegrants on performance of Simvastatin, a set of three formulations (F_9, F_{10}, F_{16}) were prepared using physical mixture of superdisintegrants (Crospovidone:Ac-Di-Sol) in three different ratios 1:1, 1:2, 1:3 respectively. The formulated tablets were subjected to various quality control tests and the results were shown in Table 13. All the tablets complied with the Pharmacopoeial standards, but F_{14} and F_{15} failed to meet the fineness of dispersion requirements. The dissolution data was presented in Figure 8. The *In-vitro* dissolution kinetics was presented in Table 14. The dissolution rate followed first-order kinetics (Figure 9) as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Simvastatin was found to be effected by physical mixture ratio's of superdisintegrants (Crospovidone and

Ac-Di-Sol) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the three formulations was F_9> F_{10}> F_{11}. The formulation prepared with physical mixture of superdisintegrants (Crospovidone : Ac-Di-Sol) in 1:1 ratio (F_{13}) was offered relatively rapid release of Simvastatin when compared with other ratios employed in this investigation. The rate of drug release was found to be increased as the concentration of the Crospovidone increases in physical mixture of Crospovidone and statistically significant difference between dissolution efficiencies (DE_{25}) of Simvastatin tablets formulated with physical mixer of superdisintegrants (Crospovidone and Ac-Di-Sol) was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are presented in Table 14. The P value was found to be less than 0.05, which indicates that there was a significant difference between F_9, F_{10}, F_{11} with respect to dissolution efficiencies (DE_{25}).

The influence of co-processed superdisintegrants on performance of Simvastatin, a set of three formulations (F_{12}, F_{13}, F_{14}) were prepared using co-processed superdisintegrants (Crospovidone : Ac-Di-Sol) in three different ratios 1:1, 1:2, 1:3 respectively. The formulated tablets were subjected to various quality control tests and the results were shown in Table 17. All the tablets complied with the pharmacopoeial standards, but F_{18} failed to meet the fineness of dispersion requirements.The dissolution data was presented in Figure 10. The *In-vitro* dissolution kinetics was presented in Table 17. The dissolution rate followed first-order kinetics (Figure 11) as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Simvastatin was found to be effected by ratio's of co-processed superdisintegrants (Crospovidone and Ac-Di-Sol) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the three formulations was F_{12}> F_{13}> F_{14}. The formulation prepared with co-processed superdisintegrants (Crospovidone: Ac-Di-Sol) in 1:1 ratio (F_{12}) was offered relatively rapid release of Simvastatin when compared with other ratios employed in this investigation. The rate of drug release was found to be increased as the concentration of the Crospovidone increases in co-processed superdisintegrants of Crospovidone and AC-DI-SOL . A statistically significant difference between dissolution efficiencies (DE_{25}) of simvastatin tablets formulated with co-processed superdisintegrants (Crospovidone and Ac-Di-Sol) was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are presented in Table 18. The P value was found to be less than 0.05, which indicates that there was a significant difference between F_{12}, F_{13}, F_{14} with respect to dissolution efficiencies (DE_{25}).

Table 1: Composition of simvastatin fast dissolving tablets formulated with Ac-Di-Sol

Sl. No.	Ingredients (mg)	F_1	F_2	F_3	F_4
1	Simvastatin	80	80	80	80
2	MCC	112	110	108	106
3	Ac-Di-Sol	4 (2%)	6 (3%)	8 (4%)	10 (5%)
4	Talc	2	2	2	2
5	Mg streate	2	2	2	2

Table 2: Composition of simvastatin fast dissolving tablets formulated with Crospovidone

Sl.	Ingredients	F_5	F_6	F_7	F_8
1	Simvastatin	80	80	80	80
2	MCC	112	110	108	106
3	Crospovidone	4 (2%)	6 (3%)	8 (4%)	10 (5%)
4	Talc	2	2	2	2
5	Mg streate	2	2	2	2

Table 3: Composition of simvastatin fast dissolving tablets formulated with physical mixer of superdisintegrants (Crospovidone: Ac-Di-Sol)

Sl. No.	Ingredients	F_9 (PM1:1)	F_{10} (PM1:2)	F_{11} (PM1:3)
1	Simvastatin	80	80	80
2	Crospovidone : Ac-Di-Sol	10	10	10
3	MCC	106	106	106
4	Talc	2	2	2
5	Mg striate	2	2	2

Table 4: Composition of simvastatin fast dissolving tablets formulated with coprocessed superdisintegrants (Crospovidone: Ac-Di-Sol)

S.NO	Ingredients	F_{12} (SE1:1)	F_{13} (SE1:2)	F_{14} (SE1:3)
1	Simvastatin	80	80	80
2	Crospovidone : Ac-Di-Sol	10	10	10
3	MCC	106	106	106
4	Talc	2	2	2
5	Mg striate	2	2	2

Table 5: Composition of simvastatin fast dissolving tablets formulated with different diluents

S.NO	Ingredients	F_{15}(SE 1:1)	F_{16} (SE 1:1)	F_{17}(SE 1:1)
1	Simvastatin	80	80	80
2	Crospovidone: Ac-Di-Sol	10	10	10
3	MCC	106	-	-
4	Mannitol	-	106	-
5	Spray dried lactose	-	-	106
6	Talc	2	2	2
7	Mg strearate	2	2	2

Table 6: Micrometric properties for formulation blends

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F_1	0.519	0.613	15.49	1.183	26.9
F_2	0.52	0.614	15.30	1.180	26.7
F_3	0.523	0.614	14.82	1.173	25.8
F_4	0.513	0.608	15.62	1.185	27.5
F_5	0.523	0.608	13.98	1.162	25.1
F_6	0.521	0.61	14.59	1.170	25.5
F_7	0.526	0.618	14.88	1.174	25.7
F_8	0.529	0.61	13.27	1.153	25.1
F_9	0.511	0.603	15.25	1.180	27
F_{10}	0.514	0.611	15.87	1.188	27.3
F_{11}	0.512	0.609	15.92	1.189	27.6
F_{12}	0.523	0.604	13.41	1.154	25.3
F_{13}	0.527	0.609	13.46	1.155	25.5
F_{14}	0.519	0.601	13.64	1.157	26
F_{15}	0.519	0.611	15.05	1.177	26.7
F_{16}	0.531	0.608	12.66	1.145	29.1
F_{17}	0.521	0.616	15.42	1.182	25.4

Table 7: Physical parameters of simvastatin tablets formulated with different concentrations of Ac-Di-Sol (F_1, F_2, F_3, F_4)

Sl. No.	Parameters	F_5	F_6	F_7	F_8
1	Average weight (mg)	198 ± 0.41	199 ± 0.23	201 ± 0.17	200 ± 0.14
2	Drug content (%)	98.76 ± 0.34	100.3 ± 0.13	99.43 ± 0.28	98.29 ± 0.32
3	Disintegration time (min)	6.4 ± 0.12	4.3 ± 0.14	3.2 ± 0.21	1.8 ± 0.17
4	Friability(%)	0.67 ± 0.23	0.74 ± 0.21	0.65 ± 0.12	0.89 ± 0.11
5	Hardness (kg/sqcm)	4.5 ± 0.45	3 ± 0.32	3.5 ± 0.45	4.0 ± 0.34
6	Wetting time (sec)	154 ± 0.32	123 ± 0.15	69 ± 0.22	83 ± 0.13
7	Water absorption Ratio	61 ± 0.43	67 ± 0.21	75 ± 0.29	87 ± 0.12
8	*In-vitro* dispersion time (min)	7 ± 0.11	4.7 ± 0.21	4 ± 0.32	2.4 ± 0.26
9	Fineness of dispersion.	Fail	Fail	Pass	Pass

Table 8: *In-vitro* dissolution kinetics of simvastatin tablets formulated with different concentrations of Ac-Di-Sol (F_1, F_2, F_3, F_4)

Sl. No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{20} (%)	K (min^{-1})	Correlation coefficient values		
						Zero order	First Order	Hixson-Crowell cube root
1	F_5	13.3	44	44	0.052	0.84	0.96	0.93
2	F_6	6.1	20.4	55.6	0.113	0.83	0.95	0.94
3	F_7	5.9	19.4	63.7	0.118	0.81	0.99	0.97
4	F_8	3.4	11.3	70.12	0.204	0.83	0.98	0.94

Table 9: Statistical treatment for dissolution efficiency of simvastatin tablets formulated with different concentrations of Ac-Di-Sol (F_1 to F_4)

Trial	Dissolution efficiencies (%) (DE_{20})				ANOVA Parameters		
	F_5	F_6	F_7	F_8	Calculated value (F)	Degree of freedom	Significance
1	44	55.6	63.7	70.1			
2	45.8	54.0	63.1	69.7	75.38	3,8	P<0.05
3	43.4	56.1	64.5	70.3			

Figure 1: Comparison of dissolution efficiency of simvastatin tablets formulated with different concentrations of Ac-Di-Sol (F_1 to F_4)

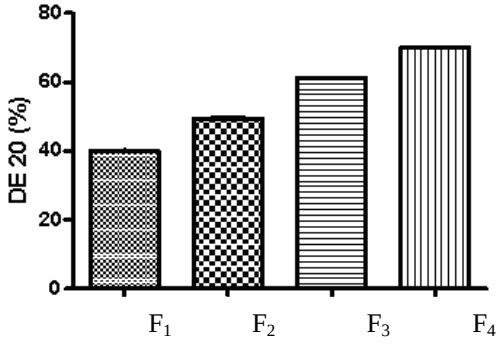
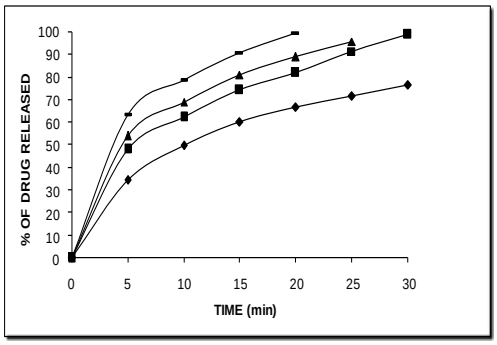
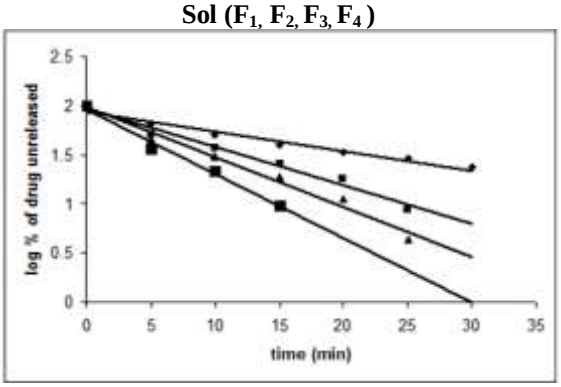


Figure 2: In-vitro dissolution profile of simvastatin fast dissolving tablets formulated with different concentrations of Ac-Di-Sol (F_1, F_2, F_3, F_4)



◊ F_1 ■ F_2 ▲ F_3 _ F_4

Figure 3: First order plots of simvastatin fast dissolving tablets formulated with different concentrations of Ac-Di-Sol (F_1, F_2, F_3, F_4)



◊ F_1 ■ F_2 ▲ F_3 _ F_4

Table 10: Physical parameters of simvastatin tablets formulated with different concentrations of Crospovidone (F_5, F_6, F_7, F_8)

Sl. No.	Parameters	F_5	F_6	F_7	F_8
1	Average weight (mg)	200 ± 0.22	198 ± 0.18	201 ± 0.24	199 ± 0.28
2	Drug content (%)	98.3 ± 0.39	99.8 ± 0.31	97.9 ± 0.29	101.6 ± 0.21
3	Disintegration time (min)	5.5 ± 0.31	3.7 ± 0.12	2.6 ± 0.21	1.5 ± 0.19
4	Friability (%)	0.82 ± 0.21	0.87 ± 0.11	0.73 ± 0.13	0.86 ± 0.18
5	Hardness (kg/sqcm)	3.5 ± 0.32	3 ± 0.45	4.5 ± 0.38	4 ± 0.21
6	Wetting time (sec)	106 ± 0.91	84 ± 0.41	58 ± 0.21	50 ± 0.53
7	Water absorption Ratio	53 ± 0.43	68 ± 0.15	70 ± 0.27	89 ± 0.35
8	In-vitro dispersion time (min)	6.9 ± 0.12	3.2 ± 0.15	3.4 ± 0.18	2.3 ± 0.11
9	Fineness of dispersion	Fail	Pass	Pass	Pass

Table 11: In-vitro Dissolution Kinetics of simvastatin Tablets Formulated With Different Concentrations Of Crospovidone (F_5, F_6, F_7, F_8)

Sl. No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values		
						Zero order	First Order	Hixson-Crowell cube root
1	F_9	5.7	19	59	0.121	0.71	0.97	0.93
2	F_{10}	3.5	11.5	64.6	0.209	0.67	0.97	0.92
3	F_{11}	2.4	7.9	70.3	0.293	0.70	0.96	0.94
4	F_{12}	2.1	7	73.6	0.330	0.80	0.99	0.95

Table 12: Statistical treatment for dissolution efficiency of simvastatin tablets formulated with different concentrations of Crospovidone (F_9 to F_{12})

Trial	Dissolution efficiencies (%) (DE_{15})				ANOVA Parameters		
	F_9	F_{10}	F_{11}	F_{12}	Calculated value (F)	Degree of freedom	Significance
1	59.5	64	70.3	73.6	267.1	3,8	P<0.05
2	58.3	64.6	71	73.9			
3	60.1	65.2	69.6	74			

Figure 4: Comparison of dissolution efficiency of simvastatin tablets formulated with different concentrations of Crospovidone (F_9 to F_{12})

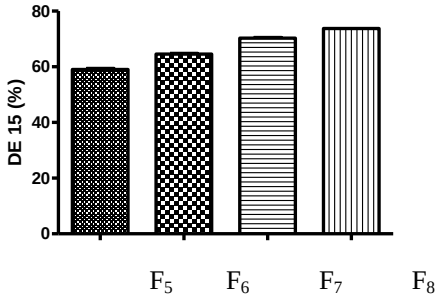


Figure 5: In-vitro dissolution profile of simvastatin fast dissolving tablets formulated with different concentrations of crosspovione (F_5, F_6, F_7, F_7)

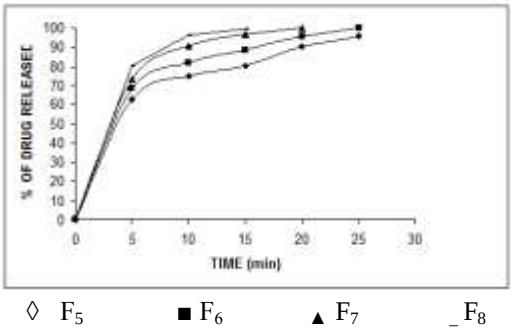


Figure 6: First order plots of simvastatin fast dissolving tablets formulated with different concentrations of Crosspovione (F_5, F_6, F_7, F_8)

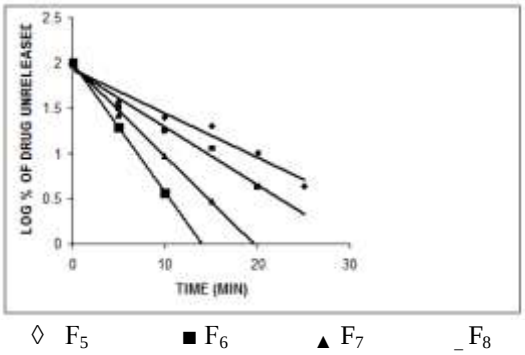


Table 13: Physical parameters of simvastatin fast dissolving tablets formulated with physical mixture of superdisintegrants (Crospovidone and Ac-Di-Sol)

Sl. No.	Parameters	F_9	F_{10}	F_{11}
1	Average weight (mg)	201 ± 0.17	200 ± 0.31	201 ± 0.26
2	Drug content(%)	96.3 ± 0.23	99 ± 0.16	99.4 ± 0.36
3	Disintegration time (min)	2.7 ± 0.36	5 ± 0.21	5.4 ± 0.17
4	Friability (%)	0.78 ± 0.27	0.88 ± 0.31	0.79 ± 0.19
5	Hardness (kg/sqcm)	3.5 ± 0.26	4 ± 0.21	3.5 ± 0.38
6	Wetting time (sec)	77 ± 0.34	83 ± 0.45	98 ± 0.23
7	Water absorption Ratio	80 ± 0.54	74 ± 0.42	67 ± 0.31
8	*In-vitro* dispersion time (min)	4.3 ± 0.11	4.5 ± 0.21	5 ± 0.29
9	Fineness of dispersion	Pass	Pass	Fail

Table 14: In-vitro dissolution kinetics of simvastatin fast dissolving tablets formulated with physical mixture of superdisintegrants (Crospovidone and Ac-Di-Sol)

Sl. No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values		
						Zero Order	First order	Hixson-Crowell cube root
1	F_9	4.6	15.2	59	0.151	0.85	0.99	0.98
2	F_{10}	7.4	24.7	45.8	0.093	0.86	0.96	0.94
3	F_{11}	15.7	52.1	30.3	0.044	0.91	0.98	0.97

Table 15: Statistical treatment for dissolution efficiency of simvastatin tablets formulated with physical mixture of superdisintegrants (Crospovidone and Ac-Di-Sol)

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_9	F_{10}	F_{11}	Calculated value (F)	Degree of freedom	Significance
1	59	45.8	30.4	1182	2,6	P<0.05
2	58.2	45	31.2			
3	59.8	46.9	32			

Figure 7: Comparison for dissolution efficiency of simvastatin fast dissolving tablets formulated with physical mixture of superdisintegrants (Crospovidone and Ac-Di-Sol)

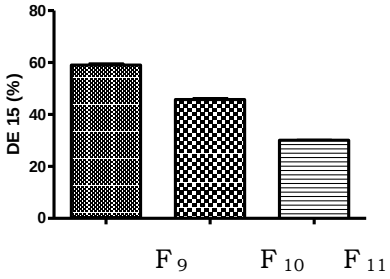


Figure 8: In-vitro dissolution profile of simvastatin fast dissolving tablets formulated with physical mixture of superdisintegrants (Crospovidone and Ac-Di-Sol)

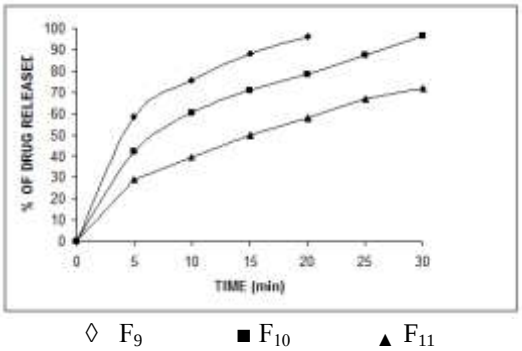
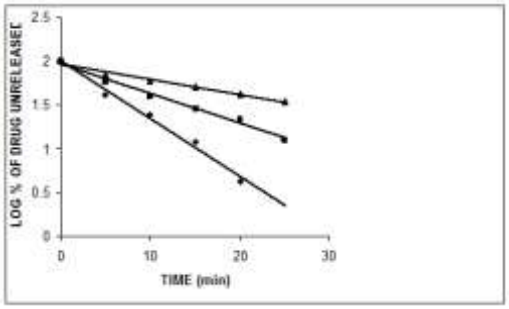


Figure 9: First order plots of simvastatin fast dissolving tablets formulated with physical mixture of superdisintegrants (Crospovidone and Ac-Di-Sol)



◊ F_9 ■ F_{10} ▲ F_{11}

Table 16: Physical parameters of simvastatin fast dissolving tablets formulated with co-processed superdisintegrants (Crospovidone and Ac-Di-Sol)

S.No.	Parameters	F_{12}	F_{13}	F_{14}
1	Average weight (mg)	198 ± 0.54	198 ± 0.29	199 ± 0.32
2	Drug content(%)	97.6 ± 0.16	97.9 ± 0.23	97.1 ± 0.31
3	Disintegration time (min)	1.4 ± 0.10	2.1 ± 0.13	3 ± 0.18
4	Friability(%)	0.94 ± 0.02	0.91 ± 0.08	0.75 ± 0.11
5	Hardness (kg/sqcm)	3 ± 0.13	3 ± 0.17	4 ± 0.19
6	Wetting time (sec)	51 ± 0.22	54 ± 0.19	62 ± 0.27
7	Water absorption ratio	96 ± 0.32	83 ± 0.31	78 ± 0.26
8	*In-vitro* dispersion time (min)	1.7 ± 0.11	3.5 ± 0.16	2.9 ± 0.13
9	Fineness of dispersion	Pass	Pass	Pass

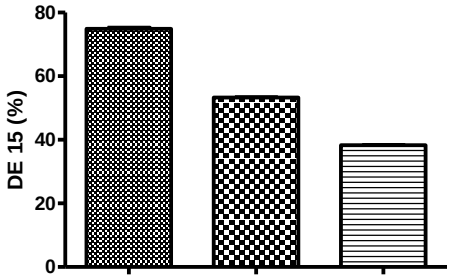
Table 17: In-vitro dissolution kinetics of simvastatin fast dissolving tablets formulated with co-processed superdisintegrants (Crospovidone and Ac-Di-Sol)

Sl. No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values		
						Zero order	First order	Hixson-Crowell cube root
1	F_{12}	2.1	7.1	74.9	0.324	0.79	0.99	0.96
2	F_{13}	6	20.1	53.3	0.114	0.81	0.95	0.95
3	F_{14}	13	43	38.3	0.053	0.82	0.95	0.92

Table 18: Statistical treatment for dissolution efficiency of simvastatin tablets formulated with co-processed superdisintegrants (Crospovidone and Ac-Di-Sol)

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_{12}	F_{13}	F_{14}	Calculated value (F)	Degree of freedom	Significance
1	74.9	53.2	38.3	3241	2,6	P<0.05
2	74	53	38.5			
3	75.8	54.1	38.1			

Figure 10: Comparison for dissolution efficiency of simvastatin fast dissolving tablets formulated with co-processed superdisintegrants (Crospovidone and Ac-Di-Sol)



F_{12} F_{13} F_{14}

Figure 11: In-vitro dissolution profiles of simvastatin fast dissolving tablets formulated with co-processed superdisintegrants (Crospovidone and AC-DI-SOL)

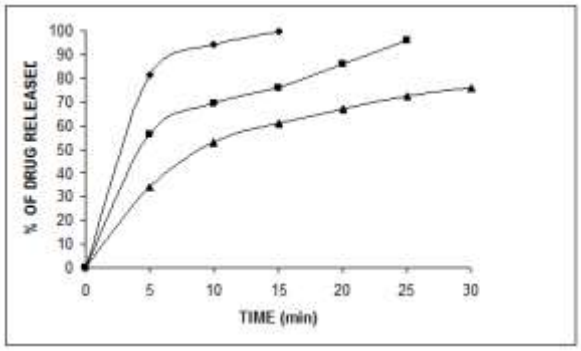
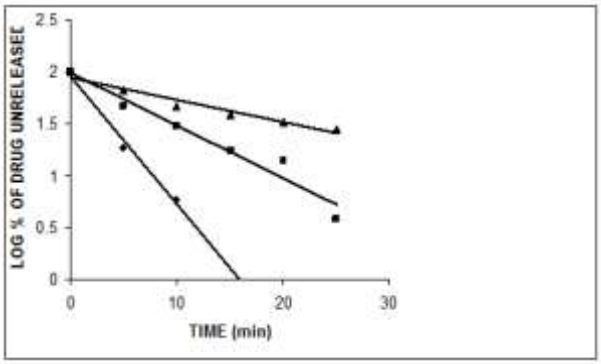
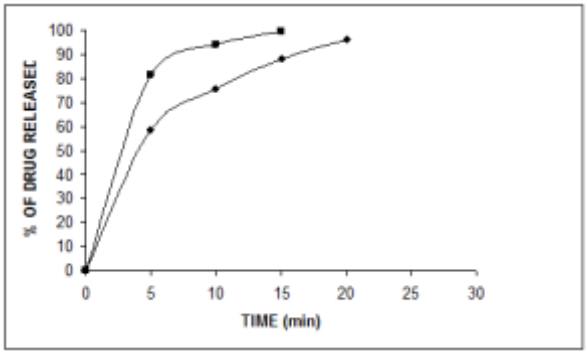


Figure 12: First order plots of simvastatin fast dissolving tablets formulated with co-processed superdisintegrants (Crospovidone and Ac-Di-Sol)



◊ F_{12} ■ F_{13} ▲ F_{14}

Figure 13: Comparative dissolution profiles of simvastatin fast dissolving tablets formulated with physical mixture of Crospovidone and Ac-Di-Sol (1:1) & co-processed Crospovidone and Ac-Di-Sol (1:1)

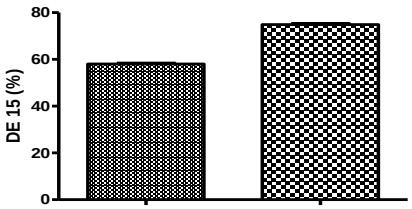


◊ F_9 ■ F_{12}

Table 19: Statistical treatment for dissolution efficiency of simvastatin tablets formulated with physical mixture of Crospovidone and Ac-Di-Sol (1:1) & co-processed Crospovidone and Ac-Di-Sol (1:1)

Trial	DE_{15} %		t table		
	F_9	F_{12}	Calculated 't' value	Degree of freedom	Significance
1	59	74.9			
2	58.2	74	21.76	4	P<0.05
3	59.8	75.8			

Figure 14: Comparison of dissolution efficiency of simvastatin tablets formulated with physical mixture of Crospovidone and Ac-Di-Sol (1:1) & co-processed Crospovidone and Ac-Di-Sol (1:1)



F_9 F_{12}

Table 19: Physical parameters of simvastatin tablets formulated with different diluents (F_{15}, F_{16}, F_{17})

S.No.	Parameters	F_{15}	F_{16}	F_{17}
1	Average weight (mg)	198 ± 0.54	199+0.19	202+0.16
2	Drug content(%)	97.6 ± 0.16	99± 0.31	98.5± 0.42
3	Disintegration time (min)	1.4 ± 0.10	2.4± 0.19	1.2± 0.23
4	Friability(%)	0.94 ± 0.02	0.6± 0.08	0.78± 0.12
5	Hardness (kg/sqcm)	3 ± 0.13	3.5± 0.15	4± 0.11
6	Wetting time (sec)	51 ± 0.22	76± 0.32	50± 0.31
7	Water absorption ratio	96 ± 0.32	85± 0.22	97± 0.41
8	In-vitro dispersion time (min)	1.7 ± 0.11	4± 0.18	1.3± 0.21
9	Fineness of dispersion	Pass	Fail	Pass

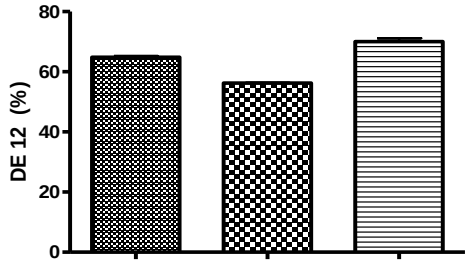
Table 21: *In-vitro* dissolution kinetics of simvastatin tablets formulated with different diluents (F_{15}, F_{16}, F_{17})

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{12} (%)	K (min^{-1})	Correlation coefficient values		
						Zero Order	First Order	Hixson-Crowell cube root
1	F_{15}	3.2	10.5	64.8	0.219	0.80	0.98	0.96
2	F_{16}	4.5	15	56.2	0.153	0.86	0.99	0.97
3	F_{17}	2.1	6.9	70	0.334	0.85	0.97	0.94

Table 22: Statistical treatment for dissolution efficiency of simvastatin tablets formulated with different diluents. (F_{15}, F_{16} and F_{17})

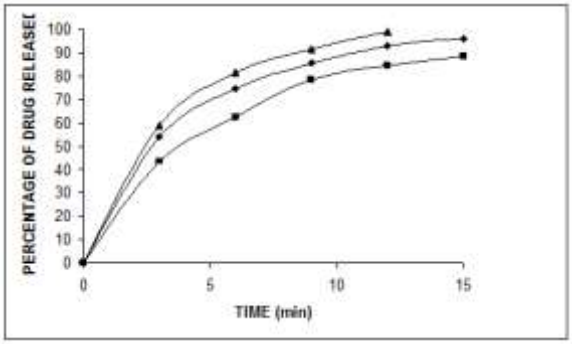
Trial	Dissolution efficiencies (%) ($D.E_{12}$)			ANOVA Parameters		
	F_{15}	F_{16}	F_{17}	Calculated value (F)	Degree of freedom	Significance
1	64.8	56.4	70.1			
2	64.3	56.8	72.2	93.41	2,6	P<0.05
3	65.2	57.2	69.6			

Figure 15: Comparison for dissolution efficiency of simvastatin tablets formulated with different diluents (F_{15}, F_{16} and F_{17})



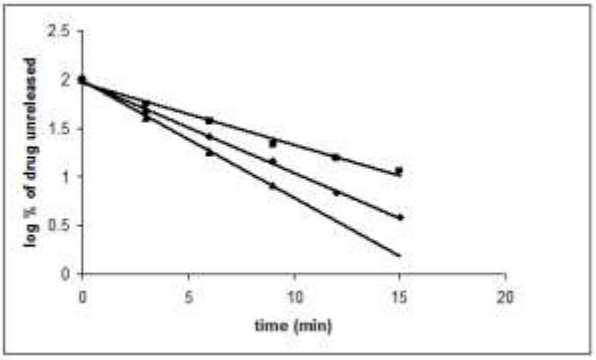
F_{15} F_{16}

Figure 16: In-vitro dissolution profile of s...h different diluents (F_{15}, F_{16}, F_{17})



◊ F_{15} ■ F_{16} ▲ F_{17}

Figure 17: First order plots of simvastatin tablets formulated with different diluents (F_{15}, F_{16}, F_{17})



◊ F_{15} ■ F_{16} ▲ F_{17}

CONCLUSION

To study the influence of pharmaceutical excipients on performance of Simvastatin, several diluents, superdisintegrants and combination of superdisintegrants at different concentrations were used to prepare acceptable Simvastatin fast dissolving tablets. Simvastatin showed P^H dependent solubility,influenced by the particle size of pure drug, can be improved by reducing the particle size.The dissolution rate was found to be influenced by nature of combination and ratio of superdisintegrants, diluents employed(Crospovidone and Ac-Di-Sol) and type of combination of superdisintegrants (physical mixing vs co-processing) employed.

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