Original Article

Preparation of Rosuvastatin Orodispersible Tablets and Comparative Evaluation with Brand and Generic Marketed Tablets

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ABSTRACT

Rosuvastatin is a type of a drug class; statins, used for treatment of high level of cholesterol and for avoid of cardio-vascular diseases. The main goals of the current study is to prepared fast dissolved tablets of rosuvastatin using different kinds of super dis-integrants to promote the dis-integration and dissolution of rosuvastatin to enhance bio-availability of a medicine. Many approaches were used to formulate a satisfactory rosuvastatin rapid dissolved tablets by using of direct compression method. The formulated tablets were characterized for different parameters, such as hardness, variation in weight , friability, time of wetting, in vitro dis-integration time and in vitro release of drug. The formulas that formulated by directly compression method showed a good flow ability .Various super dis-integrants were used including croscarmellose and crospovidone. Crospovidone is better than croscarmellose as it is showing faster dis integration time. Among the utilized diluents it was found that spray dried lactose was the best one in formulation of rosuvastatin tablets with rapid dis integration time in mouth. The best formula (F6) was formulated using 10% w/w of crospovidone, by directly compression give the lowest dis-integratoin time in the mouth (11) seconds. In additi0n to that the optimized formula had a suitable friability and hardness, therefore; it was considered as the best formulation. The net of the results showed that cr0spovid0ne was the best super dis-integrant of showing the lowest disintegrati0n time while spray dried lactose was the best diluent used in formulating of rosuvastatin oro-dispersible tablets and this suggesting the probability of utilizing the optimized best formulation (F6) in the formulation of rosuvastatin oro-dispersible tablets as a good dosage form for oraly administration.
Keywords: preparation, tablets, comparative, brand.

Introduction

The poorly water-soluble or water-insoluble molecules lists more than one third of US Pharmacopeia drugs. In new medicinal molecules development decades ago, more than 41 percent of failures are because of poor properties of bio molecules, including water insolubility, and recently, up to fifty percent of drug candidate failures have a low "drug_like" properties. The low solubility of the medicinal compounds lead to prevented absorption of drug from the site of administrati0n.[1]

To solve the above discussed problems, pharmaceutical technologists develop a Fast dissolving drug delivery tablet (Orodispersible) tablets. Rosuvastatin, as rosuvastatin calcium is 3-hydroxy—3methyl-glutaryl-CoA reeducates inhibitor used to treat the dys-lipidaemia, benign prostatic hyperplasia, osteoporosis and Alzheimers disease.resuvastatine is acrystalline in nature, therefore ;it reduces its water solubility and results in abioavailability of about 20% [(2)] .

The goal of this study is to formulate oro-dispersible rosuvastatin's tablets by using suitable of super disintegrant to promote the dis-integration and dissolution of rosuvastatin to enhance drug's bioavailability.

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Methodology

Materials

Rosuvastatin calcium(eq to rosuvastatin 10 mg), Avicel ph101, spray dried lactose,crospovidone, calcium phosphate dibasic ,aspartame,banana flavor and magnesium stearate were supplied from (sama- alfayhaa drug industry).

Methods

Characterization of Rosuvastatin

Determination of Rosuvastatin´s Melting Point.

The drug´s melting point is determine according to USP method .A little amount of medication powder was inserted into a capillary tube to create a compact 6-mercaptopurine powder column. The tube was inserted into the Stuart electrical device. Until the powder was completely melted, the temperature was taken and recorded.[3]

Determination the λ max of Rosuvastatin.

The solution of rosuvastatin of 0.1 mg/ml concentration in HCL solution medium(pH 1.2) and phosphate buffer solution (pH 6.8) were prepared, then scanned by spectrophot0meter from 200-400 nm, and the λ max of the d rug was determined.[3]

Calibration Curve of Rosuvastatin

Calibration curves were generated using drug stock solutions and series diluted concentrations of HCL solution (pH 1.2) (0.1 mg/ml for methanol and 0.01 mg/ml for HCL solution), methanol, as well as phosphate buffer solution (pH 6.8) the formulated samples were analyzed spectrophot0metrically at rosuvastatin λ max. The determined absorbance was assigned and plotted versus the concentration.[3]

The NMR Spectra

The nuclear magnetic resonance analyses were done at the laboratories of collage of sciences, Basra University. 1 H-NMR and 13C-NMR analyses were performed at 400 MHz . DMSO-d6 used as a solvent, with the chemical shifts (δ) expressed in parts per million[(4)].

Formulation of Rosuvastatin's Oro-dispersible Tablets

Orodispersible tablets were formulated as shown in Table 1 by directly compression method and before compression,all the ingredients were mixed then directly compressed by using tablet machine [(5)].

Evaluation of rosuvastatin orodispersible and marketing tablets

Pre compression Studies.

Before compression of tablets, many tests were done to make sure that the chosen excipients were compatible., differential scanning calorimetry, X-ray diffractometer and Fourier transform infrared spectroscopy were three of the other methods used to look at things. As part of formula selection, follow ability tests were also done[(6)].

Time of Wetting

The tablets wetting time were detected by putting 5 of the circular tissue´s papers (10 cm indiameter) in a suitable petridish of 10 cm in diameter. The prepared artificial saliva (10 ml) that contain methylene blue tincture (10 percent w/v) was added to the Petridish. Then the formulated tablets were transformed into the surface of tissue papers, and the time that required for the methylene dye to reach the surface of upper of a tablet was recorded and consider as a wetting time. The measurements were done in triplicate[(7)].

Hardness

The tablets needs a some am0unt of hardness or strength and must be resist the friability in order to withstand a mechanical shocks. The hardness of the tablet were detected by used of Monsanto hardness tester and the results were assigned in (Kg/cm^2) [(7,8)].

Friability

Friability of the prepared tablets were calculated by using a Roche friabilat0r. It is usually expressed in a percentage (%).

Table 1: Composition of Rosuvastatin oral dispersible Tablets

Constituents	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Rosuvastatin calcium	10	10	10	10	10	10
Avicel ph101	60	60	60	60	60	60
Crospovidone	20	30	40			
Croscarmellose sodium				20	30	40
Calcium phosphate dibasic	56	56	56	56	56	56
Aspartame	4	4	4	4	4	4
Banana flavor	2	2	2	2	2	2
Magnesium stearate	6	6	6	6	6	6
Spray dried lactose up to ….(mg)	400	400	400	400	400	400

Ten tables of each formula were firstly weighed (W, initial) and then putted in the friabilat0r. The friabilat0r usually operate at 25 rpm for four minutes or runs up to 100 revolutions. The tablets then also weighed (W final). The percent of friability was estimated by using the following equation.

$$F = \text{Initial} - \text{Final} \times 100 / \text{Initial}$$

If the percent of friability of the tablets is less than 1% is an acceptable[9].

In-vitro dis integration test

The *in-vitro* dis integration time time was estimated using dis integration test apparatus. The tablets were put inside of each 6 tubes of disintegration instrument and then add one disc in every tube. Theen the time was detected in a seconds after completion dis integration of each tablet with no palatableness mass remain in the instruments was detected in aseconds.[10]

In-vitro Dissolution Test

The dissolution of the orodispersible tablets, as well as the brand and generic marketing tablets , was done to compare the release of drugs from these formulas. All of these studies were conducted out utilizing the USP dissolution buddle method. In this method, dissolving media such as HCL solution (pH 1.2) and phosphate buffer solution (pH 6.8) were used. The stirring speed was 50 ± 2 revolutions per minute. 6-mercaptopurine was present in all formulations at a concentration of 50 mg. Each of the two mediums included 900 mL volume, which were kept at 37°C at all times.

Approximately 5 ml of the sample was taken and then filtered thr0ugh a 0.45-mm Millip0re filter at appropriate intervals (5, 10, 20, 30, 40, 50 and 60 minutes). Because of this, 5 ml of fresh dissolving solution was added to the mixture in order to keep the volume consistent. The samples were evaluated using a UV-spectrophotometer at λ max of rosuvastatin, which was used for the experiment. The drug release of each formulation was estimated by taking the average of three individual measurements.[12]

Statistical Analysis

All the results of present studies are taken as triplicate samples ± standard deviati0n and were analyzed acc0rding to the one-way analysis of variances (ANOVA) at the level of ($P < 0.05$)

Result and Discussion

Characterization of Rusuvastatin

Determination of Melting Point

There is no evidence to suggest that rusuvastatin powder is less pure than the previously reported melting point range of 180 °C.

Determination of □ max of Rosuvastatin

The UV scan of rusuvastatin in HCL medium (pH 1.2) revealed a maximum at 240.5 nm(Figure 1), which was selected as the previously published value. The UV scan of rusuvastatin in buffer medium (pH 6.8) with (Figure 2) revealed that the maximum wavelength was 241 nm[13].

Calibration Curves

Figures (3-4) illustrate the calibration curves for absorbance versus concentration, which were generated by graphing absorbance versus concentration for acidic medium and buffer medium, respectively. Given enough data and a high correlati0n coefficient of 0.999, the Beer-Lamberts equation was found to be well-confirmed for the experimental concentration range under consideration [14].

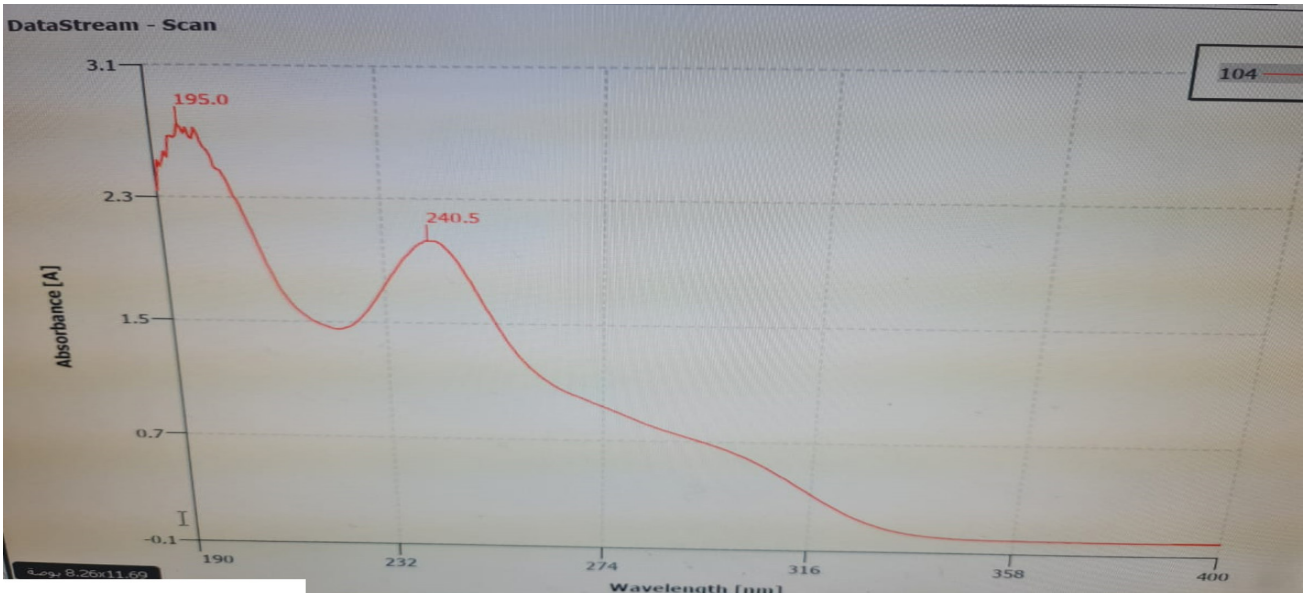

Fig. 1: UV spectra of rusovastatin in HCL solution (pH 1.2)

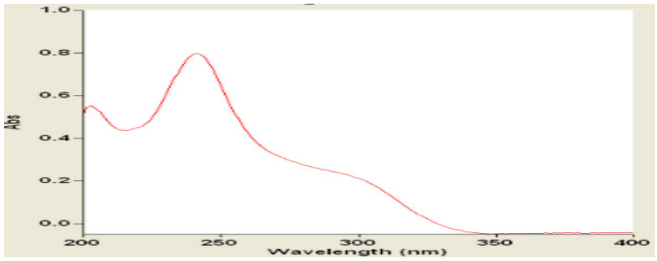

Fig. 2: UV spectra of rosuvastatin in phosphate´s buffer solution (pH 6.8)

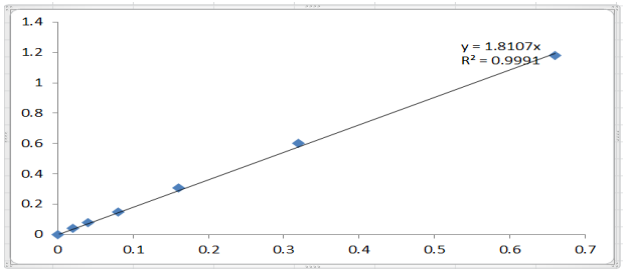

Fig. 3: Calibration curve of rosuvastatin in HCL solution (pH 1.2)

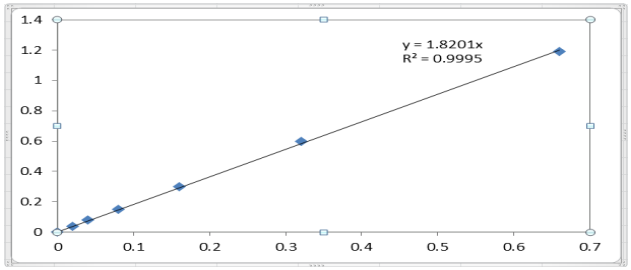

Fig. 4: CalibratiOn curve of rosuvastatin in buffer solution (p**H 6.8).**

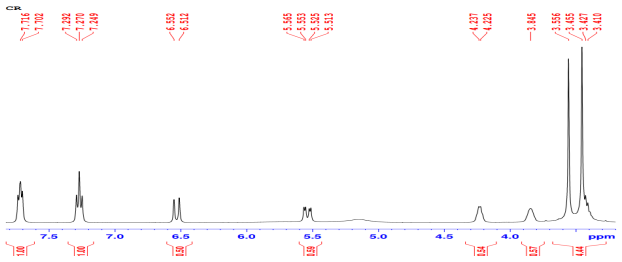

Fig. 5: 1 H NMR spectrum of rosuvastatin

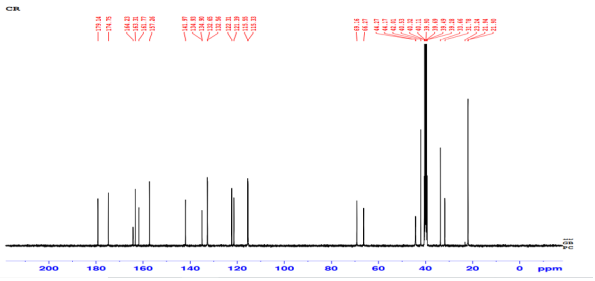

Fig. 6: ^{13}CNMR Spectrum of rosuvastatin

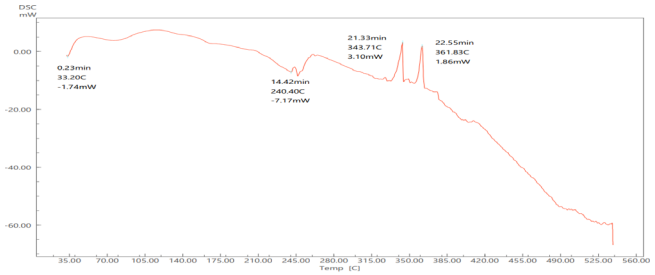

Fig. 7: DSC Thermograms of rsuvastatin

NMR Spectral Characterization

HNMR Spectroscopy

The main beaks showed by 1 H NMR spectrum, at 3.41 – 3.55ppm assigned of hydrogen atom attached to sulfur and nitrogen atom, the beaks at 3.84 ppm represent hydrogen atom in hydroxyl molecule , at 5.513 – 5.565ppm assigned of hydrogen atom in AGU part of drug and 6.5 – 7.7 ppm assigned of hydrogen atom attached to aliphatic hydrocarbon chain,[4] (Figure 7).

^{13}CNMR Spectroscopy

The 13C NMR spectrum was showed the main peaks: at 174.7, and 179.1, which were assigned to methyl group (CH3) and o—c-o., at 161- 164 were assigned to carbon atom at aromatic ring, at 69-66 were assigned of hydrogen atom in AGU part and at 21- 39 were assigned to carbon atom at aliphatic backbone and chain[(4)] as shown in figure 6 .

Differential Scanning Calorimetrical Analysis (DSC)

The prepared orodispersible tablets and its ingerdients were examined by DSC for its solid state. The crystalline behavior of free rosuvastatin is demonstrated in Figure (7) is evaluated by a single strident end0thermic peak at 240.4°C. There is only one sharp endothermic peak (19), (41). Semi-crystallinity is evident in the DSC thermographs for avicel ph 101 , calcium phosphate and spray dried lactose because of the significant endothermic peak at 351.1 °C , 205.3 °C and235.5 °C respectively[(15)] .

Thermal investigation of the optimized formulation (F5) shows a peaks of all types of excipients with a very short of the rosuvastatine a typical endothermic peak.

X-ray Diffractometric Analysis

The physical characteristics of the drug in the final formula of the drug is critical for achieving the require release pattern.[197] In this study, the physical parameters of the final formulation were determined using an XRD analysis of rosuvastatin and other excipients. Figure 13 depicts rosuvastatin X-ray diffractometric (XRD) reflections, which exhibit many distinct peaks demonstrating the drug's crystalline shape. Crospovidone and avicel ph 101 X-ray diffracti0n profile exhibits a diffuse backdrop with 2 halo diffractions, indicatingthat it is amorphous in nature.[18]

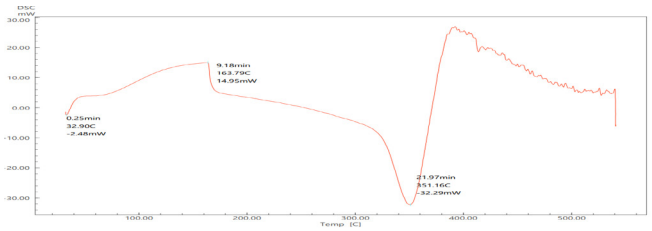

Fig. 8: DSC Thermograms of Avicel ph 101

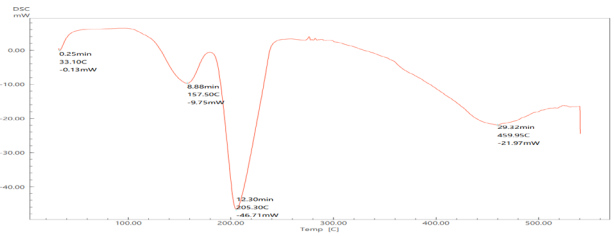

Fig. 9: DSC Thermograms of calcium phosphate

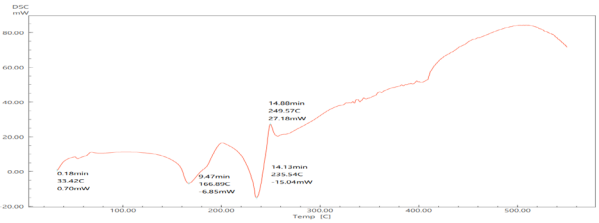

Figure10:- DSC Thermograms of spray dried lactose.

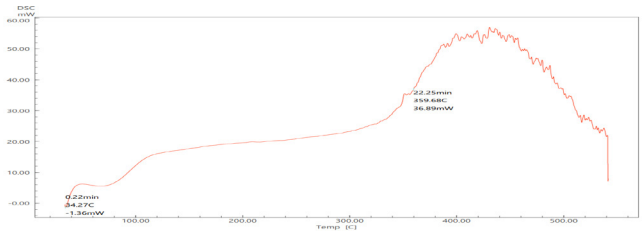

Fig. 11: DSC Thermogram of crospovidone.

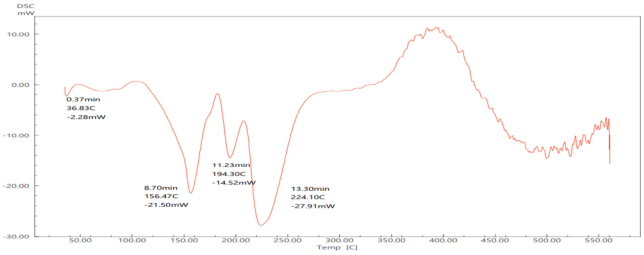

Fig. 12: DSC Thermogram of orodispersible optimized formula

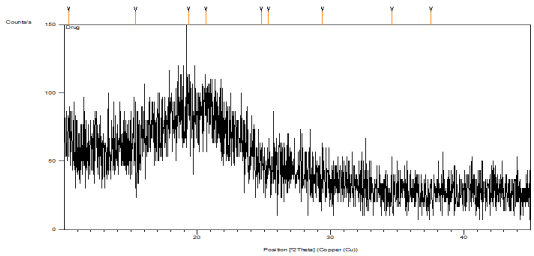

Fig. 13: X-ray-Powder diffraction of rosuvastatin

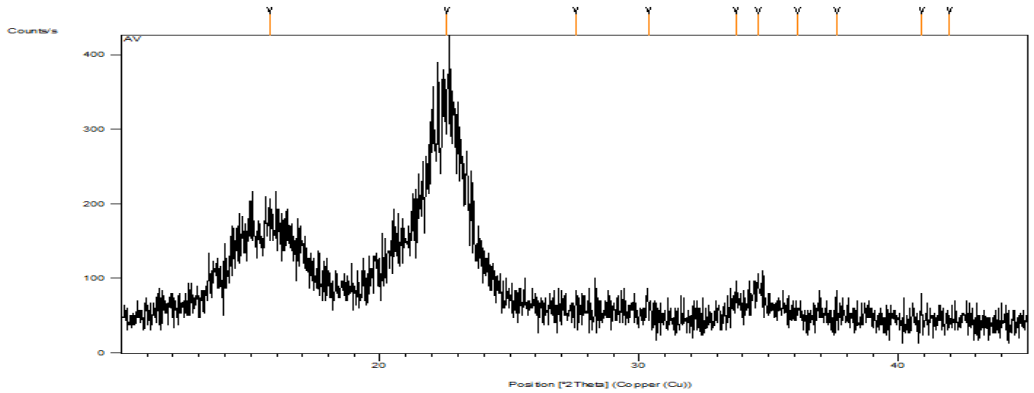

Fig. 14: X-ray-Powder diffraction of Avicel ph 101

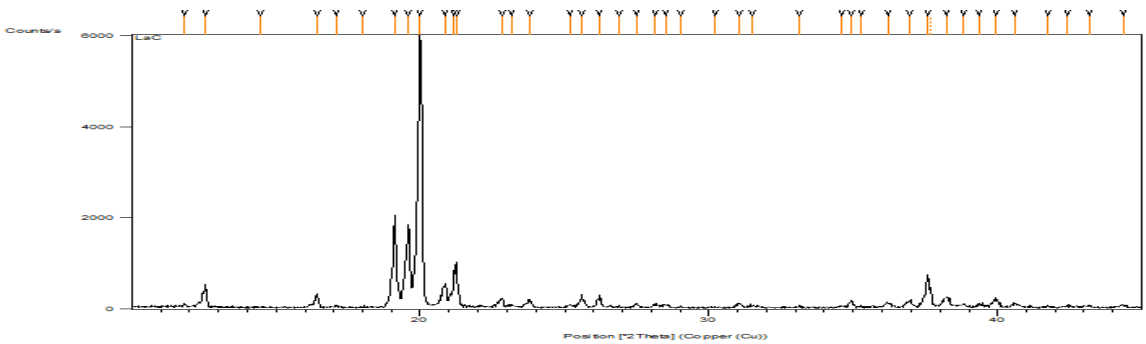

Fig. 15: X-ray-Powder Diffraction of Spray Dry Lactose.

This is not the case with spray dried lactose and calcium phosphate , which exhibits a range of reflections emphasizing the polymer's semi-crystalline structure. As illustrated in Figure (18), the spry dried and crospovidone hump in the X-ray-powder diffraction for the selected formulation (F6) reveals that the rosuvastatin crystallinity in the formula has been decreased, as previously mentioned. This was shown in the X-ray powder diffraction for the formula 6. It appears that the DSC results and the XRD data are in agreement, according to the results of the DSC.\

FTIR Spectroscopy

For the finished product to have stable, high-quality orodispersible tablets, the medication must be compatible with the excipients in the formulation. Hydrogen bonding, hydrophobic interaction, and electrostatic contact are all examples of second-order interactions that might affect compatibility [18].

Samples of spray dried lactose, Avicel pH101, pure rosuvastatin , crospovidone, calcium phosphate and optimized formula (F6) were detected by FT-IR spectrosc0pic analysis, and their spectra at 500 – 4000 cm^{-1} are sh0wn in Figures (19- 24).the characteristic peaks of N--H stretching (in aromatic group) and C= O stretching at 3338.57 cm−1 and 1548.84cm−1 appeared; respectively[18].

The characteristic bands of selected formula (F6) and other excipients are clearly visible in in selected formula (figure 24) . The pattern of optimized formulation shows that there is no interaction between the excipients and the drug. DSC and XRD measurements support this conclusion.

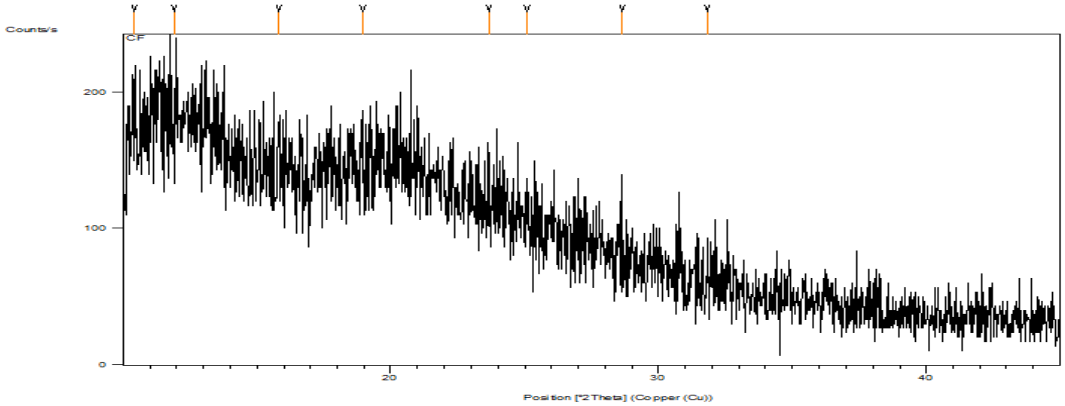

Figure 16: X-ray-Powder Diffraction of Crospovidone.

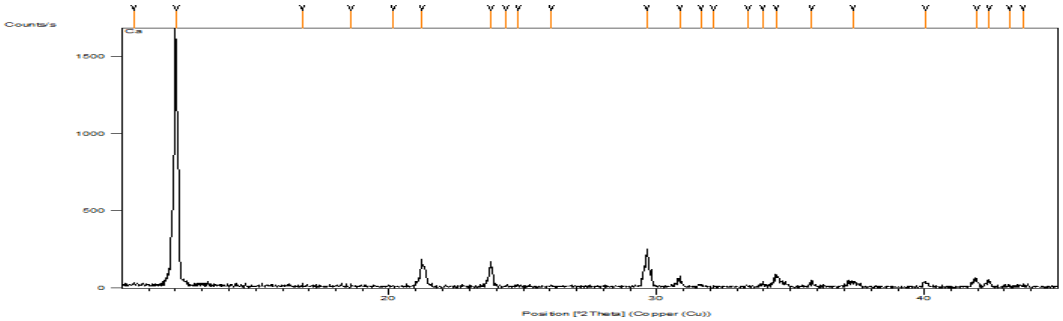

Fig. 17): X-ray-Powder Diffraction of Calcium phosphate

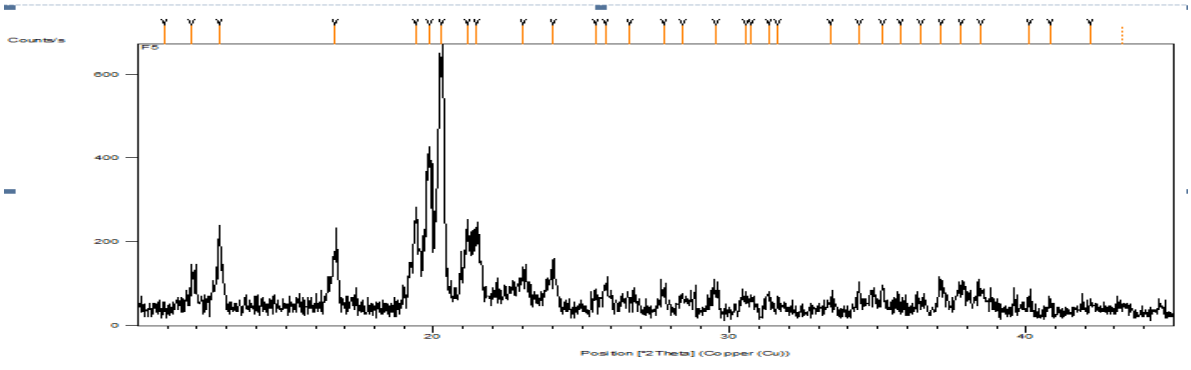

Fig. 18: X-ray-Powder Diffraction of orodispersible tablets

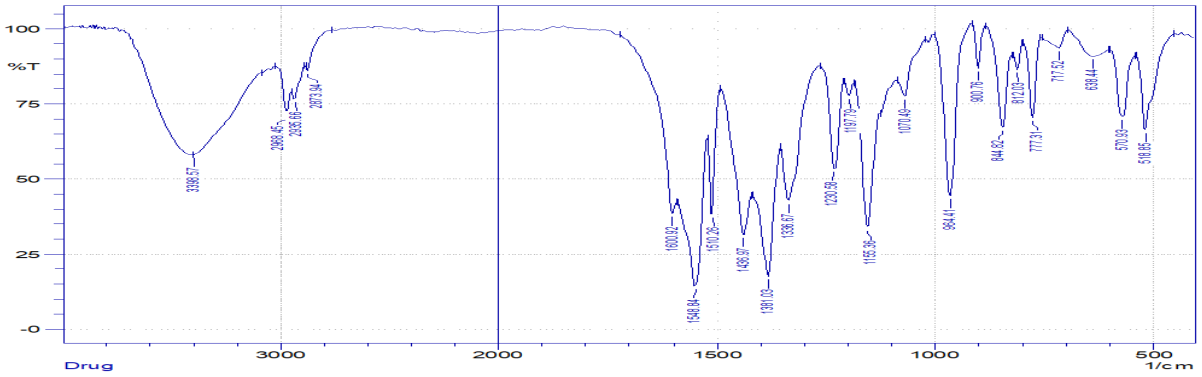

Fig. 19: FTIR Spectroscopy of Rosuvastatin

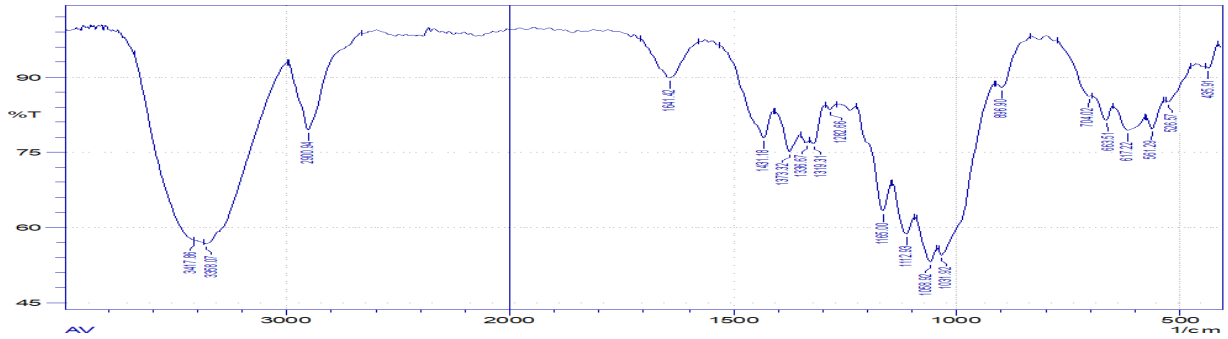

Fig. 20: FTIR Spectroscopy of avicel PH101

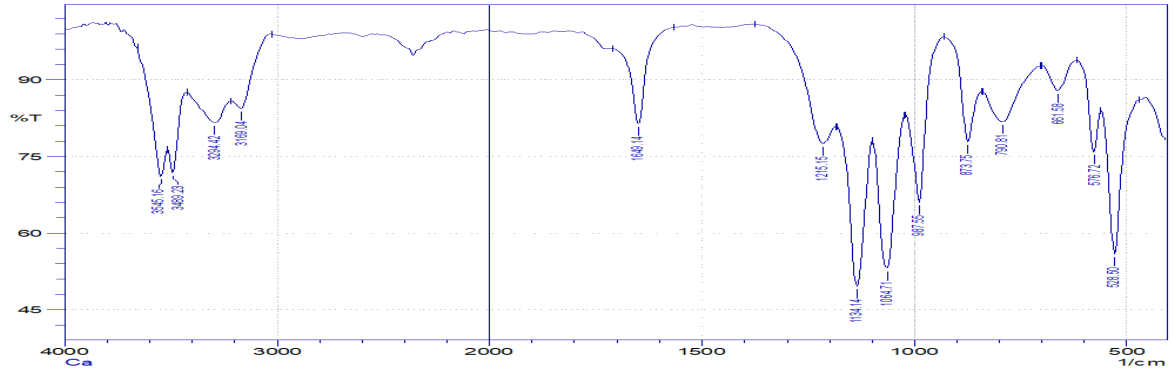

Fig0 21: FTIR Spectroscopy of calcium phosphate

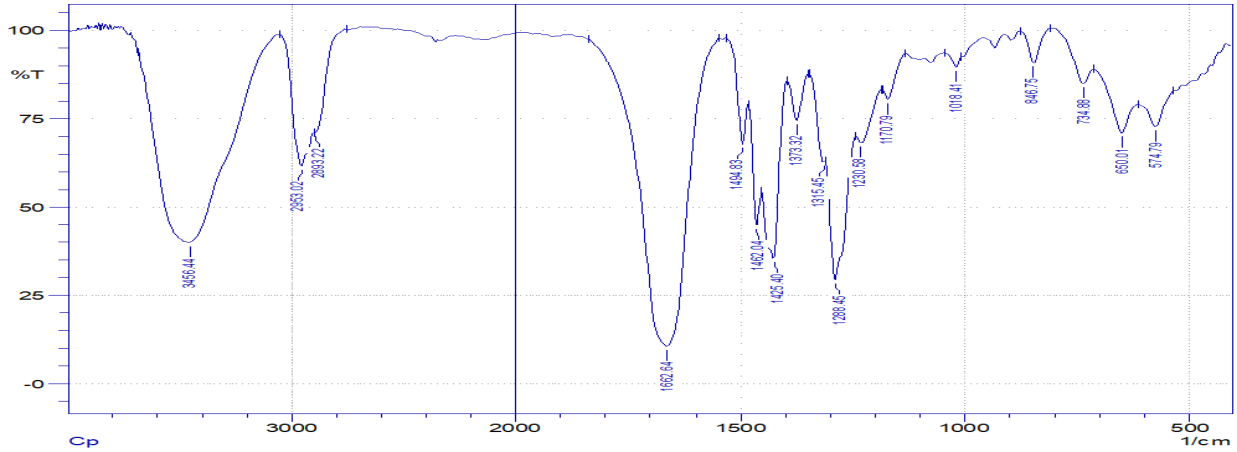

Figure 23: FTIR Spectroscopy of spray dried lactose

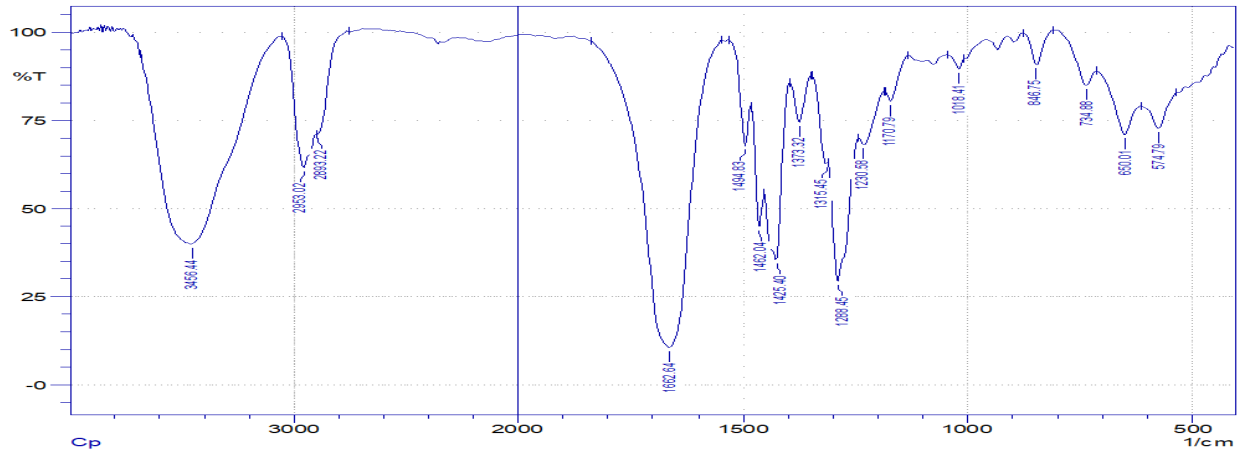

Fig. 22: FTIR Spectroscopy of Crospovidone

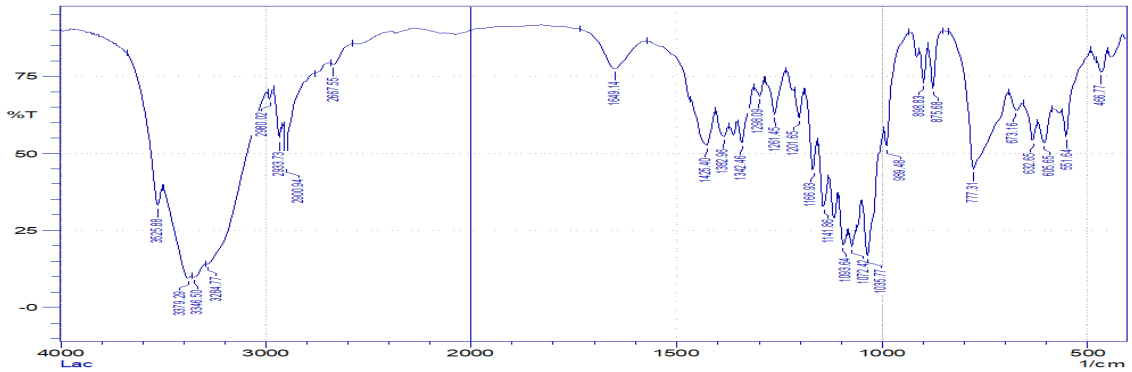

Fig. 23: FTIR Spectroscopy of spray dried lactose.

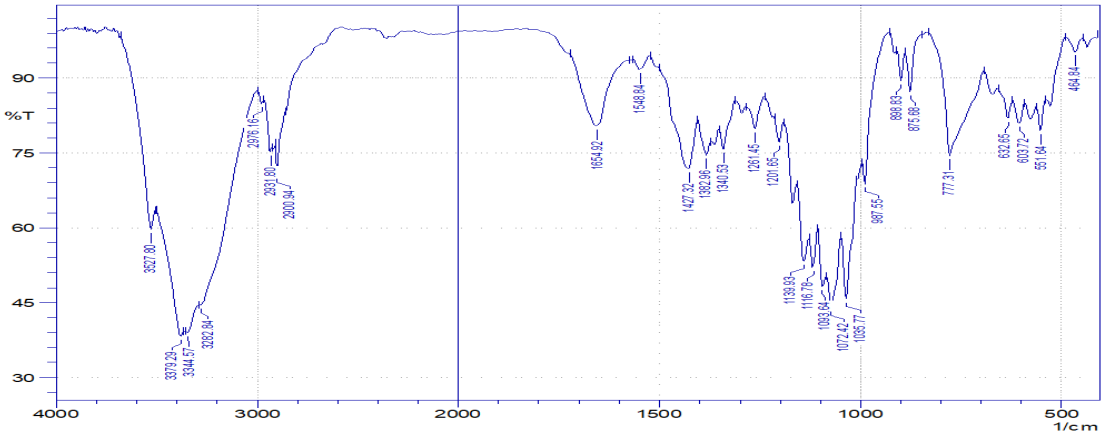

Fig. 24: FTIR Spectroscopy of orodispersible tablet .

Evaluation of powder blende

As shown in table 2 , all formulas have good flow able properties. The detected values of tapped density , bulk density. Angle of repose ,percent of compressability and Hausner ratio were within normal range. The good flow ability due to using good flow able excipient such as crospovidone, avicel ph 101 and spray dried lactose .

Evaluation of Rosuvastatin Oro-dispersible Tablet

As shown in table 3 , all formulas were within the acceptable limit regarding to hardness test ,friability test, weight variation test, diameter of tablets, time of wetting and in vitro dis integration test. The formulation number 6 show the best value for all testes ,so it was choose as the selected formula [19].

Table 2: Evaluation of powder blende

Formula code	*Bulk Density*	*Tapped Density*	*Angle of Repose*	*% of Compressibility*	*Hausner´s Ratio*
F1	0.56	0.66	25.57	15.15	1.118
F2	0.54	0.65	24.91	16.92	1.203
F3	0.53	0.61	24.54	13.1	1.15
F4	0.54	0.62	23.63	12.9	1.148
F5	0.49	0.56	26.32	12.5	1.142
F6	0.56	0.63	22.13	11.11	1.11

Table 3: Physical parameters of mouth dissolving tablets , brand and generic marketed tablets

Formula- code	*Weight Variation*	*Thickness (mm)*	*Hardness (Kg / cm2)*	*Friability %*	*Time of wetting (sec)*	*In vitro dis-integration time(sec)*
F1	pass	9.43 ± 1.02	2.4 ± 0.3	0.67 ± 0.02	40 ± 1	23 ± 2
F2	pass	10.2 ± 0.82	2.8 ± 0.2	0.68 ± 0.05	35 ± 2	19 ± 2
F3	pass	9.61 ± 0.78	2.6 ± 0.3	0.72 ± 0.04	32 ± 2	21 ± 1
F4	pass	10.01 ± 0.62	2.9 ± 0.4	0.70 ± 0.04	41 ± 6	20 ± 3
F5	pass	9.34 ± 0.56	2.7 ± 0.2	0.66 ± 0.06	33 ± 1	17 ± 1
F6	pass	9.96 ± 0.91	2.5 ± 0.2	0.69 ± 0.07	22 ± 3	11 ± 1
Brand tablet	pass	2.87 ± 0.09	5.3 ± 0.62	0.83 ± 0.05	-	174 ± 15
Generic tablet	pas	3.1 ± 0.08	5.02 ± 0.41	0.72 ± 0.06	-	234 ± 13

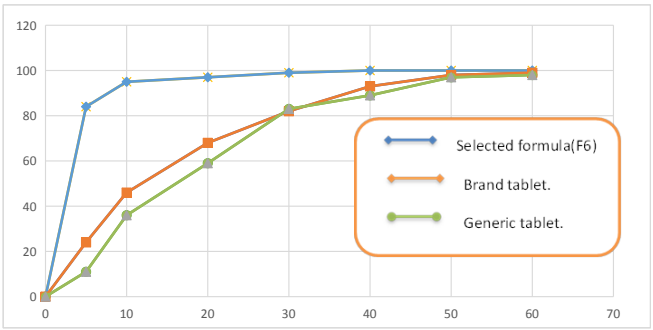

Fig. 25: The release profile of rosuvastatin selected formula F6 at 37.5 °C in buffer (pH 6.8) in contrast to the brand and generic marketed tablet

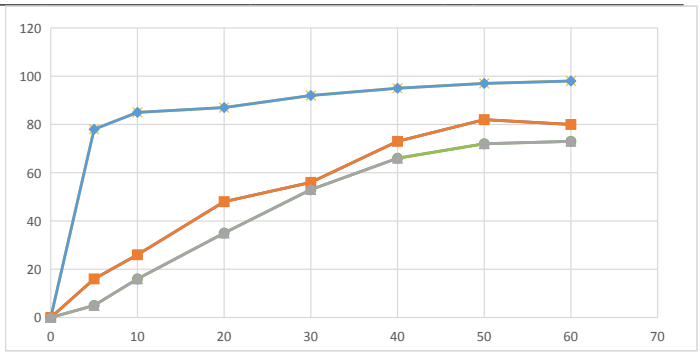

Fig. 26: The release profile of rosuvastatin selected formula F6 at 37.5 °C in 0.1 N HCL in contrast to the brand and generic marketed tablet

In-vitro Drug´s Release

In order to assessment the dissolution properties of all formulation ,the dissolution have been done in time interval of sixty minutes at 37 °C in (900) ml 0.1 N HCL and buffer system (pH 6.8). During the first five minutes , the rosuvastatin optimized formulation released 78 percent of the medication, but the generic tablet released only 5 percent of the medication and the brand tablet released only 16 percent of the medication in 0.1 N HCL dissolution medium. It took less than five minutes for the rosuvastatin-optimized formulation to release most of its active ingredient (84%) but the generic tablet released only 11percent of the medication and the brand tablet released only 24 percent of the medication in buffer system [20].

During the period of 60 minutes, all the formulas were able to release the medication in a complete pattern. As shown in figure 25 and 26. It has been demonstrated that the hydrophilic nature of crospovidone, and avicel increase in wettability and improve dissolution.

Conclusion

The best super dis integrant was a crospvidone because it showing the lowest dis integration time while spray dried

lactose was the best diluent in formulation of R0suvastatin oro-dispersible tablet. This study confirm the capability of using the optimized formulation (F5) in the formulation of orodespersible tablet of R0suvastatin as a new d0sage form for oraly rout due to the required properties of the formulated tablets regarding to enough hardness, small value of friability, rapid dis integration anddissolution.

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