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FORMULATION DEVELOPMENT AND EVALUATION OF FENOFIBRATE AND ROSUVASTATIN IN COMBINATION TABLETS AND RELEASE RATE IMPROVEMENT

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ABSTRACT: The work was aimed to develop an immediate release tablet formulation of Fenofibrate and Rosuvastatin in combination for better treatment as well as management of hypercholesterolemia and prevention of cardiovascular diseases. The target was also set to improve the dissolution profile of poorly soluble Fenofibrate. For manufacturing these immediate release combined formulation tablets, Hot-Melt Technology was used which helped in enhancing dissolution profile and moreover, here amino acids are used in conjunction with other excipients. In the developed formulation, the amino acids imparted its action as excipient by helping in the solubilization process which facilitated the release rate of Fenofibrate. The formulated tables were then investigated for hardness test, friability test, weight uniformity and dissolution test. The results showed that all tablets met the expected requirements for these tests and the release rate of fenofibrate also got improved giving an excellent dissolution profile for both fenofibrate and rosuvastatin.

INTRODUCTION: Fenofibrate is one of the most commonly prescribed fibrate class of drug that has been used since 1975 and has a well known efficacy and tolerability profile. Fenofibrate is mainly used for primary hypercholesterolemia or mixed dyslipidemia. It works by reducing low-density lipoprotein (LDL), very low density lipoprotein (VLDL) and triglycerides levels as well as increasing high-density lipoprotein (HDL) levels.[1-4]

It appears to decrease the risk of cardiovascular disease and possibly diabetic retinopathy in diabetes mellitus patients.[5]

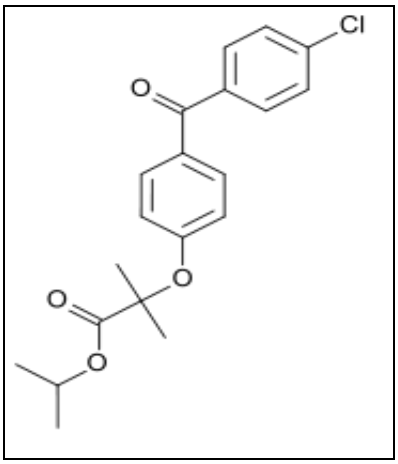

FIG. 1: STRUCTURE OF FENOFIBRATE

Chemically Fenofibrate is 1-methylethyl-2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl propanoate molecular formula $C_{20}H_{21}ClO_4$.

It is white crystalline powder stable under normal condition having molecular weight 360.83 and melting point 80-85^{0}C.[6]

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Rosuvastatin belongs to a group of drugs called HMG CoA reductase inhibitors. Rosuvastatin reduces triglycerides and low-density lipoprotein in blood by inhibiting HMG-CoA reductase while increasing the levels of "good" cholesterol or high-density lipoprotein (HDL). It is used along with exercises, supportive diet and weight-loss supplements to treat high cholesterol and related conditions, and to prevent cardiovascular disease.

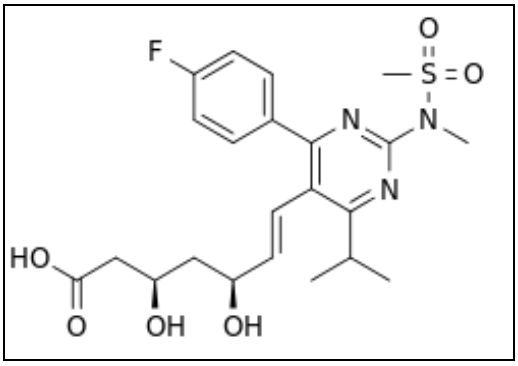

FIG. 2: STRUCTURE OF ROSUVASTATIN

Chemically Rosuvastatin is (3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid and molecular formula $C_{44}H_{54}CaF_2N_6O12S2$. It is white to off white crystalline powder having molecular weight 1001.14 and melting point 122^0C.[7]

Fenofibrate has the disadvantage of being poorly soluble in an aqueous medium which led to its having an insufficient dissolution profile. This in turn gives poor bioavailability following oral administration. Fenofibrate in combination with amino acids overcome this poor solubility and increases dissolution profile.

MATERIALS AND FORMULATION:

A combination of Fenofibrate and Rosuvastatin Calcium along with two amino acids is developed using Fenofibrate, Rosuvastatin Calcium, Microcrystalline Cellulose, Magnesium Stearate, Sodium Lauryl Sulfate, Cross Carmellose Sodium, Guar Gum, Poly Ethylene Glycol (PEG-1500), arginine, isoleucine.

A mixture of Fenofibrate, Rosuvastatin Calcium and polyethylene glycol 1500 (PEG) were physically mixed and then heated at 125°c until the mixture was completely melted to clear liquid. **Table 1** showed all the ingredients and amounts of actives and excipients used in formulation.

The hot melt liquid was stirred gently for 1 minute and then removed from the heated water bath. The mixture was allowed to cool at room temperature. Within few minutes, the mixture was Solidified. After that it was pulverized and sieved through a #14 mesh sieve (US standard mesh).

TABLE 1: THE INGREDIENTS AND AMOUNTS OF ACTIVE AND EXCIPIENTS USED IN FORMULATION

Sl	Ingredients	Amounts
1.	Fenofibrate	160 mg
2.	Rosuvastatin calcium	10 mg
3.	Microcrystalline cellulose	25 mg
4.	Magnesium stearate	2 mg
5.	Sodium lauryl sulfate	10 mg
6.	Cross carmellose sodium	7 mg
7.	Guar gum	10 mg
8.	Poly ethylene glycol (PEG-1500)	15 mg
9.	Arginine	2 mg
10.	Isoleucine	2 mg

Manufacturing of Tablet:

Sieved powders were then mixed with other excipients and blended. Using Dry granulation method the blends were compressed into tablets.

Machine Name : Xinyuan Pharmaceutical Machinary Co. Ltd. : Shanghai, Chaina ZP 35 E

Compression Force : 80 KN (Rotary tablet Press)

Tablet Dia : 9mm

RESULTS AND DISCUSSION:

Hardness Test:

The testing involved subjecting the tablets to an increasing load until the tablets break or fracture. The force was applied along the radial axis of the tablets.

Table 2 showed all test results of tablet hardness we found that the hardness for all of the tables exceed the minimum force that is 40N. So the hardness for all newly formulated tablets met the requirement.

Friability Test:

At first the tablets were weighed. Then these tablets were placed in the chamber (Veego Friability Test

Apparatus, India). The chamber was rotated for 100 times were removed. The loose dusts were cleared and the tablets were weighed again..

Percentages of Friability of the tablets were found out by the following formula:

Percentage Friability = $W1 – W_2/W_1 \times 100$

Where,

W_1 = weight of tablets before testing

W_2 = weight of tablets after testing

W_1 = 246.7 + 249.5 + 246.4 + 248.1 + 248.9 + 250.2 + 248.7 + 250.2 + 245.8 + 243.0 = 2477

Weight of tablets after testing:

W_2 = 245.9 + 248.3 + 245.6 + 245.7 + 248.0 + 244.9 + 242 + 239.5 + 248.8 + 248.9 = 2457.6

Percentage Friability = {(2477.5 - 2457.6) / 2477.5} × 100 % = 0.8032 %

For most products, the maximum weight loss of not more than 1% is acceptable,[8] so all of our tablets met the requirement as we found the average percentage of friability 0.08032.

TABLE 2: THE TEST RESULTS OF TABLET HARDNESS

Tablets Serial No.	Hardness N
1	54
2	49
3	56
4	59
5	60
6	59
7	58
8	60
9	61
10	59
11	55
12	56
13	52
14	55
15	59
16	65
17	56
18	53
19	55
20	58

Weight uniformity test: Randomly 20 tablets were selected and individual weight of each tablet is taken. The average weight was then calculated and each individual weight was compared to the average weight.

Weight of 20 tablets:

$X_1, X_2, X_3, \ldots\ldots\ldots X_{20}$

1st Tablet: 248 mg, 2nd Tablet: 247 mg, 3rd Tablet: 256 mg, 4th Tablet: 255 mg, 5th Tablet: 250 mg, 6th Tablet: 249 mg, 7th Tablet: 249 mg, 8th Tablet: 252 mg, 9th Tablet: 252 mg, 10th Tablet: 249 mg, 11th Tablet: 249 mg, 12th Tablet: 253 mg, 13th Tablet: 250 mg, 14th Tablet: 247 mg, 15th Tablet: 258 mg, 16th Tablet: 256 mg, 17th Tablet: 248 mg, 18th Tablet: 244 mg, 19th Tablet: 243 mg, 20th Tablet: 244 mg

The average weight of tablets = Total weight of tablets / Number of tablets So, the average weight of tablets, X = Total weight of tablets / Number of tablets = (248 + 247 + 256 + 255 + 250 + 250 + 249 + 249 + 252 + 249 + 249 + 253 + 250 + 247 + 258 + 256 + 248 + 244 + 243 + 244) mg / 20 = 249.85 mg

According to British Pharmacopoeia, not more than two of the individual weights deviate from the average weight by more than ± 7.5%.[8] So, all tablets met the B.P. requirement.

Dissolution Study:

Dissolution medium: 0.375% sodium lauryl sulphate solution (SLS)

USP Apparatus: #2 (Veego Dissolution test apparatus, India)

Rpm: 100

Run Time: 45 minutes

Preparation of sample solution: At first, the water bath was checked. 900 ml of 0.375% sodium lauryl sulphate solution was taken in each of the six vessels of the apparatus. The thermostat was adjusted at 37± 0.5°C. After attaining the temperature, the rotation is set to 100 rpm. One tablet was placed in each of the six vessels. The Apparatus was then operated for 45 minutes. After 45 minutes, 20ml of samples from each of the

vessels were withdrawn. The solution was then filtered and the filtrate was collected.

Preparation of standard solution: 21.1 mg of Rosuvastatin Calcium standard was taken in a 100ml volumetric flask and 60 ml of 0.375% sodium lauryl sulphate solution was added to dissolve. Finally the volume was adjusted to 100 ml by 0.375% sodium lauryl sulphate solution. Then 5 ml of this solution was taken in another 100 ml volumetric flask and then diluted to 100ml by 0.375% sodium lauryl sulphate solution. Similarly, 17 mg of Fenofibrate standard was taken in a 100ml volumetric flask. Then 60 ml of 0.375% sodium lauryl sulphate solution was added to dissolve. Finally quantity sufficient 0.375% sodium lauryl sulphate solution was added to make 100ml.

We calculated the % dissolution of Fenofibrate at 235nm by using the following equation:

$$\frac{As}{Astd} \times \frac{Wstd}{100\ ml} \times \frac{900\ ml}{L} \times \frac{P}{100} \times 100 = \%\ \text{Dissolution}$$

1. $\frac{0.403}{0.368} \times \frac{17}{100\ ml} \times \frac{900\ ml}{160} \times \frac{98.4}{100} \times 100 = 103.04\ \%$

2. $\frac{0.425}{0.368} \times \frac{17}{100\ ml} \times \frac{900\ ml}{160} \times \frac{98.4}{100} \times 100 = 108.67\ \%$

3. $\frac{0.417}{0.368} \times \frac{17}{100\ ml} \times \frac{900\ ml}{160} \times \frac{98.4}{100} \times 100 = 106.62\%$

4. $\frac{0.406}{0.368} \times \frac{17}{100\ ml} \times \frac{900\ ml}{160} \times \frac{98.4}{100} \times 100 = 103.81\%$

5. $\frac{0.414}{0.368} \times \frac{17}{100\ ml} \times \frac{900\ ml}{160} \times \frac{98.4}{100} \times 100 = 105.86\%$

6. $\frac{0.417}{0.368} \times \frac{17}{100\ ml} \times \frac{900\ ml}{160} \times \frac{98.4}{100} \times 100 = 106.62\%$

We calculated the % dissolution of Rosuvastatin at 286 nm by using the following equation:

$$\frac{As}{Astd} \times \frac{Wstd \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{L} \times \frac{P}{100} \times 100 = \%\ \text{Dissolution}$$

1. $\frac{0.197}{0.222} \times \frac{21.1 \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{10} \times \frac{90.41}{100} \times 100 = 76.17\%$

2. $\frac{0.207}{0.222} \times \frac{21.1 \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{10} \times \frac{90.41}{100} \times 100 = 80.04\%$

3. $\frac{0.204}{0.222} \times \frac{21.1 \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{10} \times \frac{90.41}{100} \times 100 = 78.88\%$

4. $\frac{0.197}{0.222} \times \frac{21.1 \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{10} \times \frac{90.41}{100} \times 100 = 76.17\%$

5. $\frac{0.203}{0.222} \times \frac{21.1 \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{10} \times \frac{90.41}{100} \times 100 = 78.49\%$

6. $\frac{0.205}{0.222} \times \frac{21.1 \times 5}{100 \times 100\ ml} \times \frac{900\ ml}{10} \times \frac{90.41}{100} \times 100 = 79.27\%$

According to USP, In case of immediate/conventional-Release Drug Products, for six tablets, each unit is not less than 75%. So, all of our tablets meet the USP requirements of immediate-release tablets.

CONCLUSION: The formulation for combination tablet of Fenofibrate and Rosuvastatin was developed. Here, isoleucine and arginine worked as solubility enhancers, significantly increasing the release rate of Fenofibrate. All results implied that using hot-melt technology and amino acids as excipients significantly improved the dissolution profile.

REFERENCES:

1. Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. J Cardiovasc Pharmacol 2011; 57(2):267-72.
2. Lee M, Saver JL, Towfighi A, Chow J, Ovbiageli B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis 2011; 217(2):492-8.
3. Tenenbaum A, Medvedovsky D, Fisman EZ, Bubyr L, Matetzky S, Tanne D, et al. Cardiovascular events in patients received combined fibrate/statin treatment versus statin monotherapy: acute coronary syndrome Israeli surveys data. PLoS ONE 2012; 7(4):e35298-7.
4. Accord Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362(17):1562-74.
5. Hermans MP. Impact of fenofibrate on type 2 diabetes patients with features of the metabolic syndrome: subgroup analysis from FIELD. Curr Cardiol Rev2010; 6(2):1128.
6. http://chemicalland21.com/bioscience/bp/FENOFIBRATE.htm
7. http://www.emedicinehealth.com/drug-rosuvastatin/article_em.htm
8. British Pharmacopeia. The Pharmaceutical Press, Her Majesty's Stationery Office, London. 1998; Vol. I. pp. 379, 969, 1242.

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