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Design, Characterisation and Evaluation of Sustained Release Formulation of Remogliflozin Etabonate

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A B S T R A C T

Now-a-days Type 2 diabetes mellitus is a very crucial common disease and emerging condition that glucose level of Human body cannot be controlled. In case of Type-2 diabetes mellitus, pancreas does not produce enough insulin. In such a condition, we have to thing for a medicament for treating the disease; Remogliflozin Etabonate is such type of drug that efficacious and safe agent that we can administer in our body. The Half-Life of the drug is 120 minutes.This research has taken into consideration on improving the release pattern of the drug by sustaining its action at maximum level of time, using the different ratios of Polymer and discusses the individual studies performed during its development for design, characterization and evaluation of analytical and formulative profile, as well as *in-vitro* Characterization. In that case, this research work is hopefully very much useful for further proceeding and for large scale aspect in industrial point of view.

Keywords: Type 2 diabetes mellitus, Remogliflozin Etabonate, Analytical Profile, Formulative Profile, *in-vitro* Characterization, Half-life.

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INTRODUCTION:

Remogliflozin Etabonate is an antidiabetic drug. The structural name of Remogliflozin Etabonate is ethyl[(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6[5-methyl1--propan-2- yl-4- [(4- propan-2- yloxyphenyl) methyl] pyrazol-3-yl] oxyoxan-2-yl] methyl carbonate. Remogliflozin Etabonate is prodrug of Remogliflozin, with benzylpyrazole glucoside based inhibitor of renal SGLT2 with antihyperglycemic activity. [01, 02]

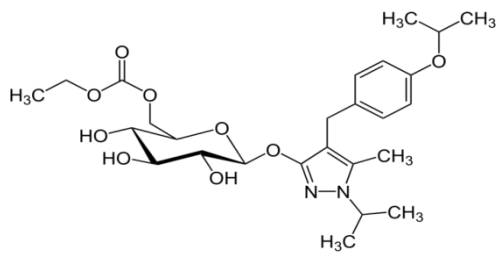


Figure 1: Structure of Remogliflozin Etabonate

The terminal half-life for Remogliflozin Etabonate is 1.53 h. Following single oral administration at 100 and 250 mg, Remogliflozin Etabonate showed favorable, linear pharmacokinetics. So, our main motive of the research is to sustain the action of Remogliflozin Etabonate by decreasing the frequency of the dose. For quality control, a suitable analytical approach for assaying these anti-diabetic medicines is necessary. [3]

Insulin is a Sugar-Regulating hormone to the cells. The pancreas does not produce enough insulin. The cells cannot respond or respond poorly to insulin and take in less sugar. [4] Moreover according to clinical trials of the phase – III of FDC as well as bioequivalence studies of Remogliflozin Etabonate is used to improve the glycaemic control. [5]

Materials and methods: The proposed method was developed and validated in Laboratory by

1. **Analytical Studies-**
   Description, Solubility, Thin Layer Chromatography, UV Spectroscopy Analysis, Infrared Analysis of the drug, Melting Point, Standard Curve, Drug-Excipient Interaction Study [By IR], Excipient Identification Test, Assay of drug.

2. **Preformulation Studies-**
   Bulk Density, Tapped Density, Hausner Ratio, Percent Compressibility, Angle of Repose [without Talc], Angle of Repose [with Talc], Physical Compatibility Test
   Formulation [wet granulation].

3. **Post Formulation Studies [*in-vitro* Studies]-**
   General Appearance, Size & Shape of Tablets, Hardness, Friability, Disintegration Test, Weight Variation, Dissolution Test, Assay Parameter.

1. **Analytical Study-**
   a. Description- Remogliflozin Etabonate Drug is found to be white powder.
   b. Solubility- Remogliflozin Etabonate is soluble in Methanol, Ethanol and Dimethyl sulfoxide (DMSO). Remogliflozin Etabonate is insoluble in Purified Water and also insoluble in Hot Water.
   c. Thin Layer Chromatography- at first the solvent system was prepared as a same ratio of Ethyl Acetate, Hexane and Methanol. The sample solution was prepared as- 100mg of Drug was dissolved in Methanol and volume was made up to 100ml. Then 1ml solution was withdrawn from the stock solution and volume was made up to 10ml.
   d. The TLC plate was prepared and applied on the plate. The spot was detected under UV light and Fluorescence light.
   e. UV Spectroscopy Analysis- The drug was prepared at 10µg/ml concentration. Then the maximum wavelength of the drug was found to be 228nm.
   f. Infrared Analysis of the drug (IR)- The Infrared Analysis of the drug was done in AT-IR and sample curve was determined. The result was found to be that, the wavelength of 'OH' functional group 3288nm, the wavelength of 'C=O' functional group 1745nm and the wavelength of 'C-O' functional group 1100nm. 'OH' functional group tends to 'H' bond (intra or intermolecular bond), that's why it may changes.
   g. Melting Point- The drug was placed to the Melting point apparatus and measured the value that the drug was started to melt.
   h. Standard Curve- The sample solution was made and places into UV-Vis Spectrophotometer at different concentration like 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/m, 60µg/ml, 70µg/ml, 80µg/ml, 90µg/ml, and 100µg/ml. lastly the absorbance of each solution was measured at 228nm.
   i. Drug-Excipient Interaction Study [By IR]- The drug-excipients interactions study was done by IR spectroscopy (chemical method). The result was found to be same as per to be that, the wavelength of 'OH' functional group 3288nm, the wavelength of 'C=O' functional group 1745nm and the wavelength of 'C-O' functional group 1100nm. 'OH' functional group tends to 'H' bond (intra or intermolecular bond), that's why it may changes.
   j. Excipient Identification Test- Excipients identification test was done as per the Indian Pharmacopoeia basis for PVP-K30, Microcrystalline Cellulose, Talc, Hydroxypropyl methyl cellulose, Magnesium Stearate.
   k. Assay of drug- The assay of drug was done by UV-visible spectroscopy method, as the concentration was 10µg/ml.

2. **Preformulation Studies-** Preformulation studies were done by following methods for lubricated bulk powder.

   a. Bulk Density- The bulk density was done the initial of lubricated powder. The Formula was followed by:

   b. Bulk density (ρ_b) =Mass of the powder [M]/ Volume of the powder [V]

   c. Tapped Density- after Tapping, the tapped density was done the final of lubricated powder. The Formula was followed by:

   d. Tapped density (ρ_t) =Mass of the Tapped powder [M]/ Volume of the Tapped powder [V]

   e. Hausner Ratio: It is calculated from the ratio of tapped density and bulk density.
   f. $H_r = \rho_{tap}/\rho_b$
   g. Percent Compressibility: Percent Compressibility is determined from the following formula: $100\times[(\rho_{tap}-\rho_b)/\rho_{tap}]$
   h. Angle of Repose [without Talc]- Angle of Repose is determined by the following formula before introducing Talc;
   i. $\Theta=Tan^{-1}$ [H/R]; where H= height of the heap of the powder and R= radius of the powder; Θ= angle is created due to flow property of the powder.
   j. Angle of Repose [with Talc]- Angle of Repose is determined by the following formula after introducing Talc;
   k. $\Theta=Tan^{-1}$ [H/R]; where H= height of the heap of the powder and R= radius of the powder; Θ= angle is created due to flow property of the powder.
   l. Physical Compatibility Test- Physical compatibility test is done for the drug and drug with excipients with a particular ratio and kept in different temperatures. Then no colour change is found and that is absolutely perfect result for the study.

3. **Formulation [wet granulation] -** The formulation for the drug was designed as wet granulation method. The drug is hygroscopic and Loss on Drying of the drug is also high. So, the method of tablet preparation was introduced. Total 6 batches of the drug as sustained release formulation is prepared by ranging of polymers.

4. **Post Formulation Studies [*in-vitro* Studies] -** Post formulation studies of the formulated six batches was studied as per Indian Pharmacopoeia and also noted.

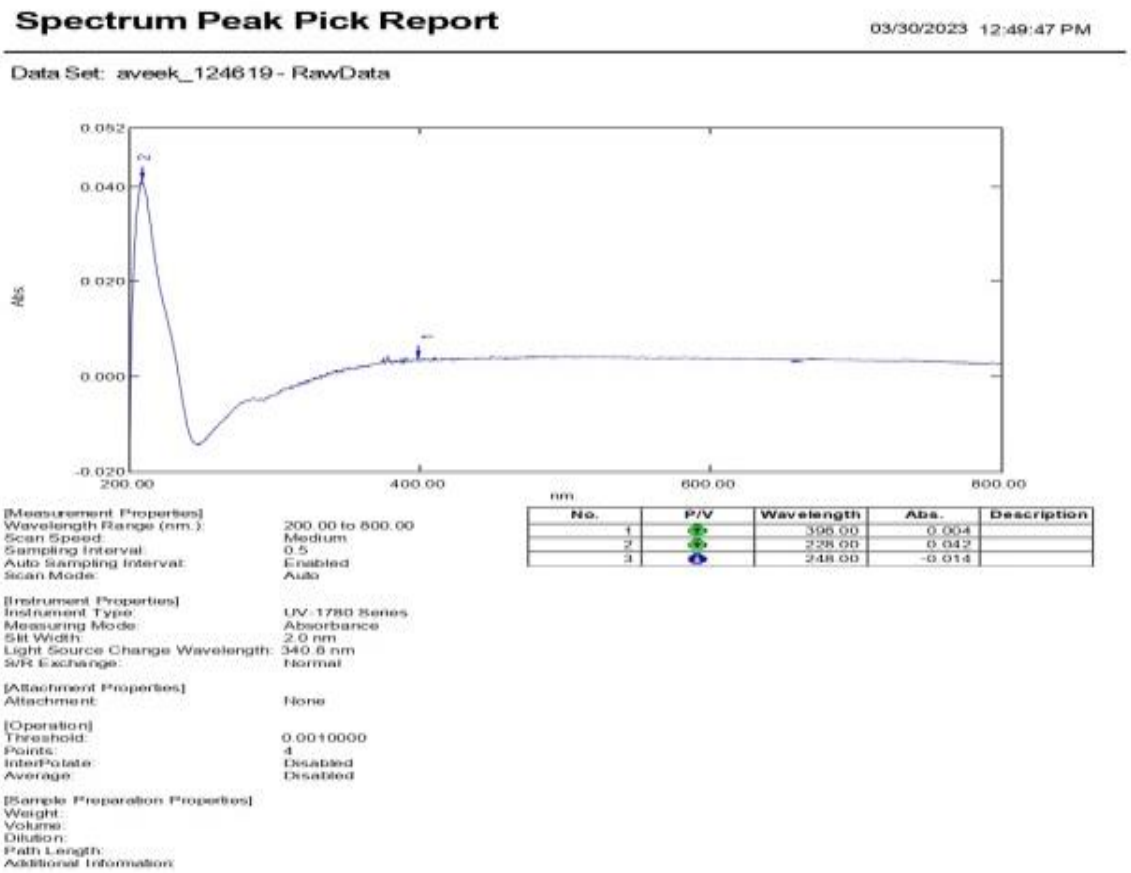
a. General Appearance- General Appearance of the formulated six batches in each tablet was examined like colour, odour.
b. Size & Shape of Tablets- Size, shape of the formulated six batches in each tablet was examined and noted.
c. Hardness- Hardness of the tablets of each batch was determined by Monsanto Hardness tester. The Unit of the Hardness test is kg/cm^2.
d. Friability- Friability test of the each batch was determined by Roche friabilator. The formula for determining the result is- $[W_2-W_1]/W_1$.
W_2= Final weight after revolution,
W_1= Initial weight before revolution.
The result should be within 0-1%.
e. Disintegration Test- Generally the Disintegration Time Test is not done for Sustained release Tablets. But for the research purpose the Disintegration test was done DT machine at particular time.
f. Weight Variation- Weight variation was done as per Indian Pharmacopoeial method.
g. Dissolution Test- Dissolution test (i.e. % of drug release) was done in each formulated batch by UV-Vis Spectrophotometric method and result with graphical representation was noted.
h. Assay Parameter- Assay [drug content] of the each formulated batch was done by UV-Vis Spectrophotometric method.

Table 1: Formulation Table

FORMULATION TABLE						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
REMOGLIFLOZIN ETABONATE [mg]	100	100	100	100	100	100
PVP-K30 [mg]	9	9	9	9	9	9
MICROCRYSTALLINE CELLULOSE [mg]	71.4	61.4	51.4	41.4	31.4	21.4
MAGNESIUM STEARATE [mg]	3.6	3.6	3.6	3.6	3.6	3.6
HPMC-K15 [mg]	60	70	80	90	100	110
TALC [mg]	6	6	6	6	6	6
Total [mg]	**250**	**250**	**250**	**250**	**250**	**250**

RESULTS AND DISCUSSION

a. Description- Remogliflozin Etabonate is a Whitish Powder.
b. Solubility- Remogliflozin Etabonate is in Methanol, DMSO; but insoluble in water and also hot Water.
c. TLC- The calculated R_f VALUE is 0.50.
d. UV Spectroscopy Analysis- the Maximum Wavelength (λ_{max}) of Remogliflozin Etabonate is found to be that 228nm.
e. IR Analysis- The result was found to be same as per to be that, the wavelength of 'OH' functional group 3288nm, the wavelength of 'C=O' functional group 1745nm and the wavelength of 'C-O' functional group 1100nm. 'OH' functional group tends to 'H' bond (intra or intermolecular bond), that's why it may changes.
f. Melting Point- Melting Point of the drug is found to be 97℃-98℃.
g. Standard Curve- The standard curve was determined at pH 1.2 HCl Buffer and R^2 value was found to be 0.9996.
h. Drug-Excipient Interaction Study [Chemical Parameter-IR]- Drug-Excipient interaction study was done by IR Spectrum.
i. Excipient Identification Test- Complies as per colour change method by Indian Pharmacopoeia.
j. Assay of Drug-The Assay of the drug was done by UV Vis- Spectrophotometric method and found to be 97.561 %W/W.
k. Bulk Density- Bulk density was found to be F1-0.476, F2- 0.436, F3- 0.4, F4- 0.382, F5- 0.382, F6- 0.412.
l. Tapped Density- Tapped density was found to be F1-0.518, F2- 0.5, F3- 0.456, F4- 0.528, F5-0.436, F6- 0.436.
m. Hausner Ratio- Hausner Ratio was found to be F1-1.09, F2- 1.146, F3- 1.14, F4- 1.16, F5-1.141, F6- 0.436.
n. Percent Compressibility [%]-Percent Compressibility was found to be F1-8.11, F2-12.8, F3- 12.28, F4- 14.07, F5- 12.39, F6- 13.45.
o. Angle of Repose [Without Talc] -Angle Of Repose [Without Talc] was found to be F1-28.7, F2- 29.25, F3- 26.1, F4- 26.41, F5- 29.31, F6-29.11.
p. Angle of Repose [With Talc] - Angle Of Repose [With Talc] was found to be F1-22.12, F2-23.01, F3- 22.14, F4- 22.55, F5- 22.32, F6-23.22.
q. Physical Compatibility Test- There was no change and also known as physically incompatible with each other.



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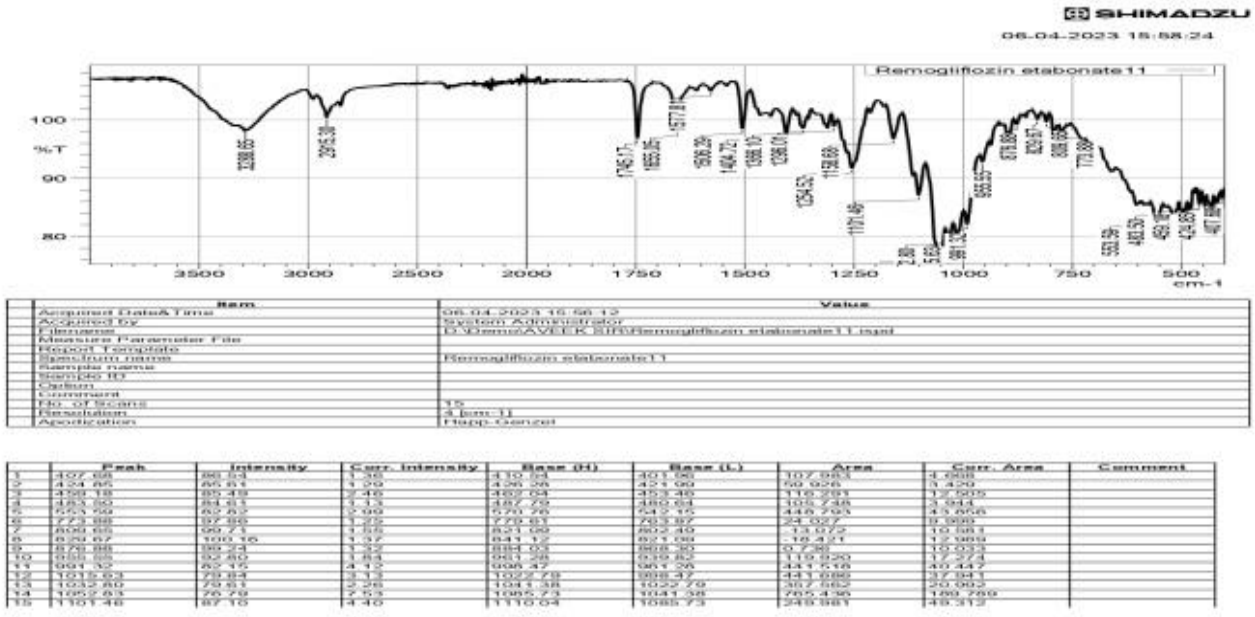

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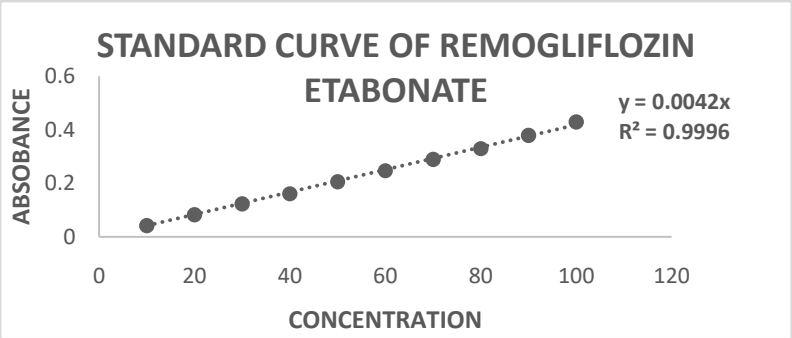

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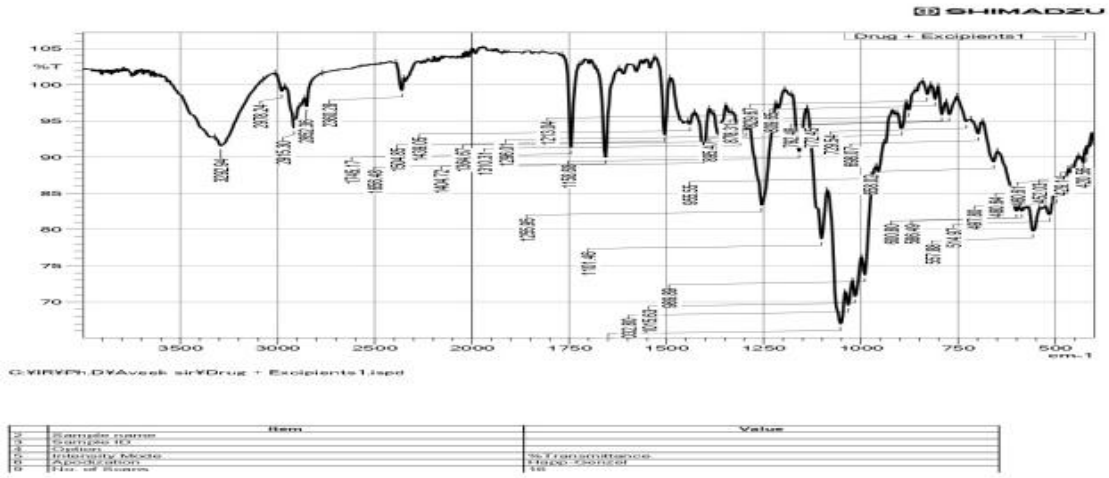

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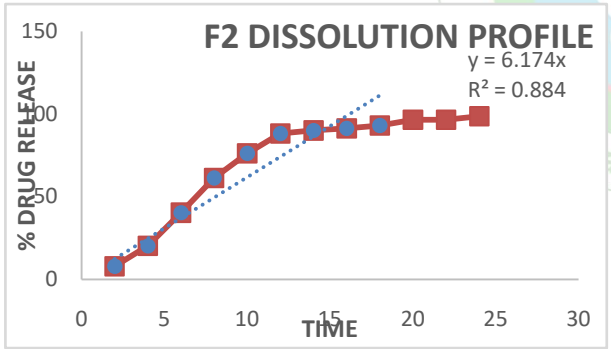

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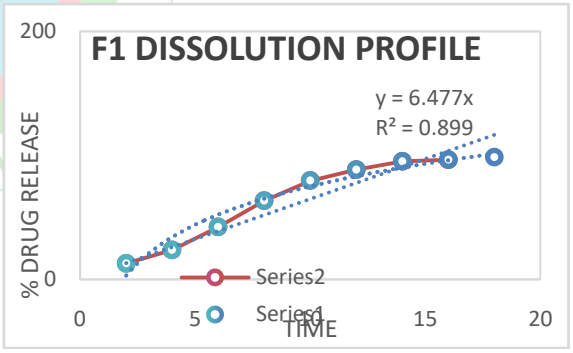

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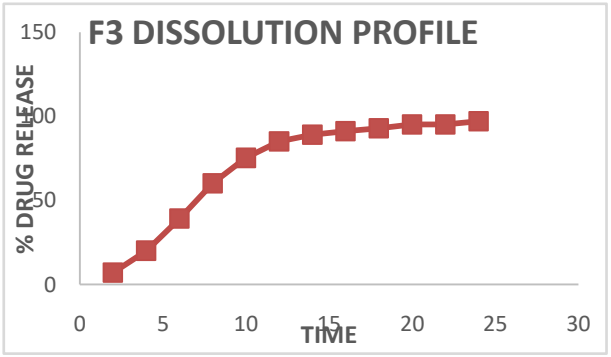

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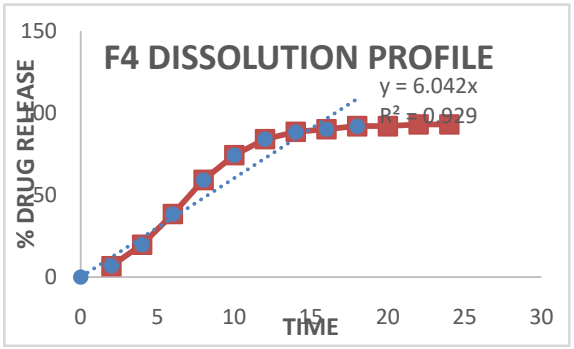

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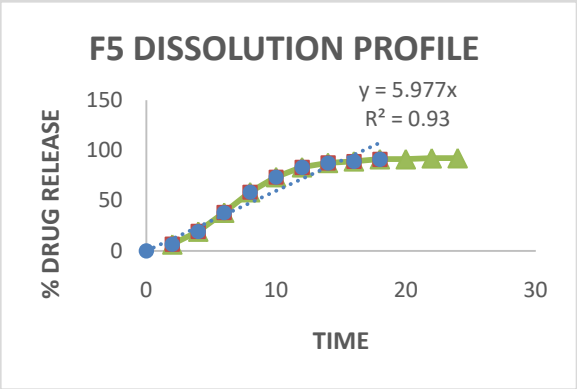

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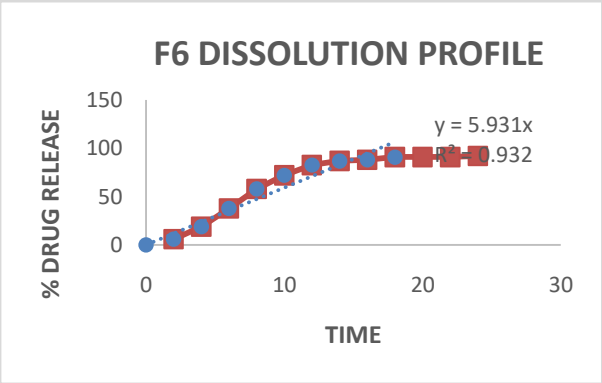

Figure 11:

CONCLUSION-

This research has taken into consideration on improving the release pattern of the drug by sustaining its action at maximum level of time, using the different ratios of Polymer and discusses the individual studies performed during its development for design, characterization and evaluation of analytical and formulative profile, as well as *in-vitro* Characterization. The drug has short half-life, 120 minutes; it has been sustained in more than 24 hours. It can easily be concluded that the work has been almost successfully established.

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Conflict Of Interest- It is an entity or individual becomes unreliable because of a clash between personal interests and professional .

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