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Pharmaceutical Sciences **Research Article……!!!**

"STUDY OF EFFECT OF FENUGREEK EXTRACT AS A SUPERDISINTEGRANT IN THE FORMULATION OF REPAGLINIDE FAST DISSOLVING TABLETS"

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KEYWORDS:

Fast dispersible Tablet, Repaglinide, Direct compression, Natural Superdisintegrants (*Fenugreek seed mucilage*).

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ABSTRACT

Difficulty in swallowing is common among all age groups, especially elderly and pediatrics. Orally dispersible tablets may constitute an innovative dosage form that overcome the problem of swallowing and provide a quick onset of action. This study was aimed to formulate and evaluate fast dissolving tablets (FDTs) containing Repaglinide using synthetic Superdisintegrants (Sodium starch glycolate and crospovidone) and natural Superdisintegrant (Fenugreek seed mucilage). The prepared tablets were evaluated for hardness, friability, thickness, drug content uniformity, wetting time, disintegration time, and cumulative amount of drug release after 30 minutes. According to the evaluation studies, the best selected formulation (F6) containing a natural Superdisintegrants showed the faster disintegration time (34 - 48 secs) and % drug release (95.25% in 30 mins) as compared to other super disintegrating agent. So, *Fenugreek seed mucilage* a natural Superdisintegrants, gives a rapid disintegration and high release when compared with synthetic Superdisintegrants in formulation of FDTs.

INTRODUCTION:

Diabetes mellitus is one of the most common chronic diseases in nearly all countries and continues to increase in numbers and significance, as changing lifestyles lead to reduced physical activity and increased obesity.[1]

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia or raised blood sugar is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

Meglitinides (glinides) make up a class of drugs used to treat diabetes type II. They bind to an ATP-dependent K^+ (KATP) channel on the cell membrane of pancreatic β-cells in a similar manner to sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site. This increases the concentration of intracellular potassium, which causes the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granulate with the cell membrane and therefore increased secretion of (pro) insulin. Repaginate (REP), 2-ethoxy-4-[2-[[(1S)-3-methyl-1-[2-(1-piperidinyl) phenyl] butyl] amino]-2-oxoethyl] benzoic acid is an oral ant diabetic drug, which was developed to specifically control meal-related glucose fluctuations in patients with type Ⅱ diabetes mellitus by stimulating insulin secretion from the pancreas With a low water solubility (34 mg/ml at 37°C) and high lipophilicity (log P ¼ 3.97), REP belongs to Biopharmaceutical classification system (BCS) class II drug. So, there are challenges on increasing the dissolution and bioavailability of the drug. However, there is a certain degree of difficulty in formulation and preparation technologies to improve the dissolution of REP by the methods mentioned above, which brings a great challenge to the preparation production in industry[2]

MATERIALS ANDMETHODS

Materials:

Repaglinide gift sample obtained from Micro lab ltd, Sodium starch glycolate from Yarrow Chem products Mumbai, Crospovidone from Balaji drugs, Fenugreek seed from Local market, Microcrystalline cellulose, Magnesium Stearate, Mannitol from Thomas Baker Chemicals Pvt.Ltd.

Preparation of Fenugreek Seed Mucilage

Collected Trigonella foenum-graecum was carefully washed and dried under sun for 1-2 days. Fenugreek seeds (50 gm) were powdered through grinder and stored in air tight container for further use.

Step 1: Extraction of mucilage

Powder soaked in distilled water (300 ml) for 24 hours in a round bottomed flask. It was boiled for 1 hr. under reflux with occasional stirring and kept aside for 2 hrs for the release of mucilage into water. The

material was filtered through a muslin bag and hot distilled water (50 ml) was added through the sides of the marc and squeezed well in order to remove the mucilage.

Step 2: Isolation of mucilage

Extracted mucilage has isolated in acetone. Equal volume of Acetone was added to the filtrate in order to precipitate the mucilage and kept aside a refrigerator for one day for effective settling. It was filtered and dried completely in an incubator at 37°C, powdered, weighed and stored in desiccators for further use.

Characterization of Fenugreek seed mucilage powder:

1 .Loss on drying: 1.0 gm of the sample was transferred into 3 petridishes and then dried in an oven at 105^{O}C until a constant weight was obtained. The percentage loss of moisture on drying was calculated using the formula and expressed as a percentage.

LOD (%) = (weight of water in sample/ weight of dry sample) x 100

2.Swelling index:

One gram of FSM powder (#120 meshes passed) was accurately weighed and transferred to a 100 ml stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100 ml mark with distilled water. The cylinder was stoppered, shaken gently and set aside for 24 h. The volume occupied by the mucilage sediment was noted after 24 hours. It is expressed as a percentage and calculated according to the following equation:

Swelling index (SI) = Xt –Xo/ Xt x 100=2-1/ 2 x 100= 50%

Where, Xo= initial height of the powder in graduated cylinder.

Xt = the height occupied by swollen gum after 24 h.

The content from the measuring cylinder from the above test were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100 ml graduated cylinder.

The volume of water collected was noted and the difference between the original volume of the mucilage and the volume drained was taken as water retained by sample and was referred to as water retention capacity or water absorption capacity[3]

Drug–polymer compatibility studies

The FTIR spectra of pure drug, drug combined with polymers and natural super disintegrates were measured using Fourier Transform Infra-Red Spectrophotometer. Pure drug and drug combined with polymers were separately mixed with IR grade KBr and converted into KBr pellet by hydraulic press and scanned over a range of 4000 to 400 cm^{-1}.[4]

Preparation of Repaglinide solid dispersion:

Solid dispersion of Repaglinide in PEG6000 was prepared by solvent evaporation method as below:

Solvent evaporation method:-

Ingredients: Repaglinide, PEG 6000, Methanol.

Procedure:

Drug and polymer were mixed in the ratios (1:1, 1:3 & 1:5) in a glass mortar. Methanol was addedportion-wise with constant continuous stirring until the mixture completely dissolved. Methanol was evaporated under reduced pressure & the resultant solid dispersion was collected.

Characterization of solid dispersion of Repaglinide with PEG 6000

Dissolution Studies:

Dissolution studies of Repaglinide in powder form, SDs were performed by using USP Type 2 paddle apparatus at paddle rotation speed of 75 rpm in 900 ml of 6.8 phosphate buffers as a dissolution medium at 37±0.5°C. The solid dispersion equivalent to 2mg of Repaglinide was weighed using digital balance & added in to the dissolution medium. At the specified times (every 5 min for 30 minute), 1 ml samples were withdrawn by using syringe filter(0.45µm) by measuring the absorbance at 283 nm using uv visible spectrophotometer.

Preparation of Fast dissolving tablets of Repaglinide by direct compression method

Repaglinide fast dissolving tablets were prepared by direct compression method by using super disintegrants like Sodium starch Glycolate, Crospovidone, Fenugreek seed mucilage. Microcrystalline Cellulose used as diluents, Aspartame used as a sweetening agent, Magnesium Stearate, Talc used as a lubricant and glidants. All the ingredients (except granular directly compressible excipients) were passed through # 80-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of drug as well as other components and compressed into tablets of 200 mg round flat punches on rotary tablet compression machine.

Table-1: Composition of fast dissolving tablets of Repaglinide containing 3 Superdisintegrants

S.No	**Ingredients(mg)**	**F1**	F2	F3	F4	F5	F6	F7	F8	F9
1.	1:5 Solid dispersion equivalent to 2mg Repaglinide	10	10	10	10	10	10	10	10	10
2.	Micro crystalline cellulose	92	92	92	92	92	92	92	92	92
3.	Mannitol	80	78	76	80	78	76	80	78	76
4.	Sodium Starch Glycolate	10	12	14	-	-	-	-	-	-
5.	*Fenugreek Seed* Mucilage	-	-	-	10	12	14	-	-	-
6.	Crospovidone	-	-	-	-	-	-	10	12	14
7.	Aspartane	1	1	1	1	1	1	1	1	1

8.	Magnesium stearate	5	5	5	5	5	5	5	5	5
9.	Talc	2	2	2	2	2	2	2	2	2

All quantities are in milligrams (mg) only

Pre-formulation evaluation

Determination of angle of repose:

Angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

Determination of Bulk Density and Tapped Density

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

$$\text{Bulk density} = W / V_o$$

The bulk density, and tapped density were calculated using the following formulae.

$$\text{Tapped density} = W / V_F$$

Where, W = weight of the granules,

V_O= initial volume of the granules,

V_F = final volume of the granules.

Hauser's Ratio:

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density[5].

$$\text{Hauser's Ratio} = \text{Tapped density/Bulk density}$$

Compressibility index (Carr's Index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20% has good flow property.[5]

POST COMPRESSION EVALUATION

Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Pfizer hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability (F)

Friability of the tablet was determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

The friability (F) is given by the formula.

$$\% \text{ Friability} = \frac{\text{initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Venire Calipers. It was determined by checking the thickness of three tablets of each formulation.[6]

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the.

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$Dl/dt = r\Upsilon\cos\theta/ (4\eta l)$$

Where l is the length of penetration, r is the capillary radius; Υ is the surface tension, η is the liquid viscosity, t is the time, and θ is the contact angle.

Procedure:

A double folded tissue paper should be placed in a petridish containing 6 ml of Phosphate buffer 6.8. The tablet was kept on the paper and the time for complete wetting of the tablet was measured in units of seconds.[7]

Disintegration test:

The *in vitro* disintegration studies were carried out using Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±2 ^{o}C. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded.

***In vitro* drug release:**

Release of the drug *in vitro*, was determined by estimating the dissolution profile, USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, phosphate buffer (pH 6.8) (900 ml) was used as a dissolution medium.[8]

RESULTS

Determination of λmax and Standard Calibration Curve for Repaglinide

λ max of Repaglinide was found to be 283 nm as it shows maximum absorbance in this wavelength

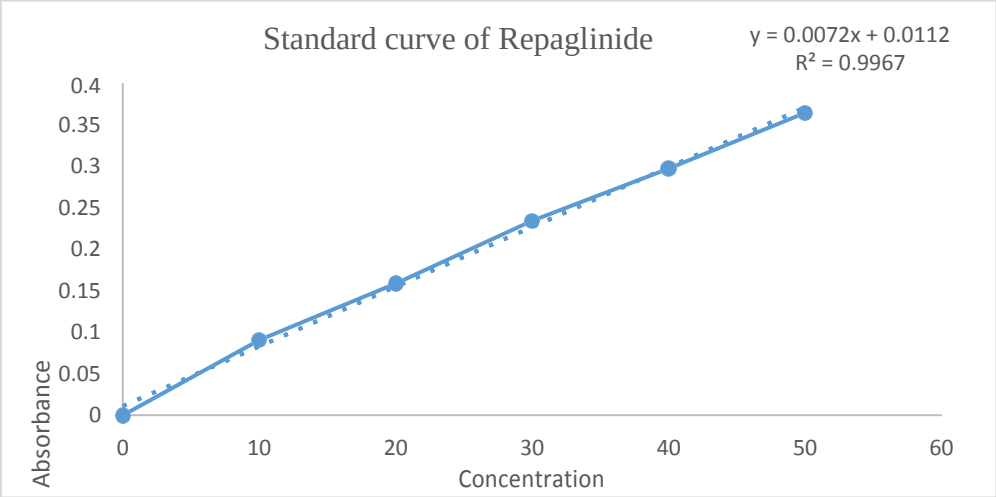

Fig 1: Standard calibration curve of Repaglinide in 6.8 Phosphate buffer.

Characterization of Fenugreek seed mucilage powder:

1. **Loss on drying**: The percentage loss of moisture on drying was calculated using the formula and expressed as a percentage. It was found to be 24.19%.
2. **Swelling Index**: Swelling index (SI) is expressed as a percentage. It was found to be 50%.

Preparation of solid dispersion

As per the method given above, solid dispersion was prepared.

Characterization of solid dispersion of Repaglinide with PEG 6000

Dissolution studies

Table No 2: *In-vitro* Dissolution profile of Repaglinide solid dispersion in pH 6.8 buffers.

Formulation	**Percentage drug release after 30 minutes (DR)**
Drug	45.55 ± 2.25%
SD 1:1	79.70 ± 2.27 %
SD 1:2	89.58 ± 2.35%
SD 1:3	96.81 2.71%

Drug and excipients compatibility studies by FT- IR Spectroscopy.

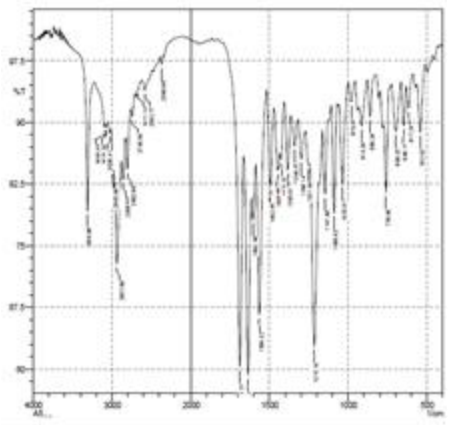

Figure 2: FT-IR spectrum of drug Repaglinide alone

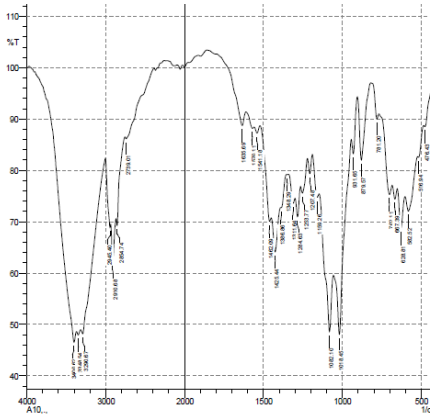

Figure 3: FT-IR Spectra of F6 Formulation

Compatibility study of drug with excipients

Physical mixture of drug and polymer was characterized by FT-IR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Repaglinide were found to be unaltered in the drug-excipients physical mixtures, indicating they were compatible chemically.

DISCUSSION

Pre-formulation studies of powder blends:

For each type of formulation blends of API and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.41-0.54 g/cm^3 and the tapped density between 0.45-0.60 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between (10-16.36) %, the compressibility and flow ability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from angle of repose so the angle of repose was

found to be in the range of 18.26-29.03^0. Angle of repose below 30º indicates good flow property. The Hausner's ratio was found to be 1.11-1.19. In the present study it's revealed that all powder blends showed good flow property.

Pre- compression parameters of Repaglinide fast dissolving tablets

All the FDT formulations were evaluated for their thickness using Vernier callipers as per procedure.

Tablet hardness is critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage. All FDT formulations were evaluated for their hardness as per procedure in methodology section 4.6.1 and the results recorded. All the formulations have an average hardness in between 2.63 to 3.38 kg/cm^2 which was found to be acceptable; because these formulations have to be disintegrated on the tongue between 25 seconds to 1 minute. So excess of hardness is not favored for these formulations. The hardness for F8 (3.38 Kg/cm^2) was found to be highest of all formulations and for F6 (2.63 Kg/cm^2) was found to be least. The average percentage friability for all the formulations was in the range of 0.43% to 0.65%, which was found to be within the limit (i.e. maximum 1%). So the maximum friability was 0.65% and the minimum friability 0.43% observed for F6 and F1 respectively.

. All the formulated FDTs of Repaglinide were evaluated for their wetting time as per the procedure in methodology. The average wetting time for all the formulations was in the range of 28±0.62 to 44±0.35 seconds. The maximum wetting time of 44 seconds and minimum wetting time of 30seconds were shown by F7 and F3 respectively.

As material was free-flowing tablets obtained were uniform weight due to uniform die fill with acceptable variation as per IP standards. The maximum weight was found to be 200.66 mg for F4 and the minimum observed was 196.66 mg for F6. The maximum allowed percentage weight variation for tablets 80-250 mg by I.P is 7.5%, and no formulations are exceeding this limit. Thus all the formulations were found to be complying with the standards given in IP.

The average *in-vitro* disintegration time for all the formulations were in the range of was 34 -48 seconds. The lowest *in-vitro* disintegration time for formulation F6 was 34 seconds and highest disintegration time was found to be formulation F7 was 48 seconds.

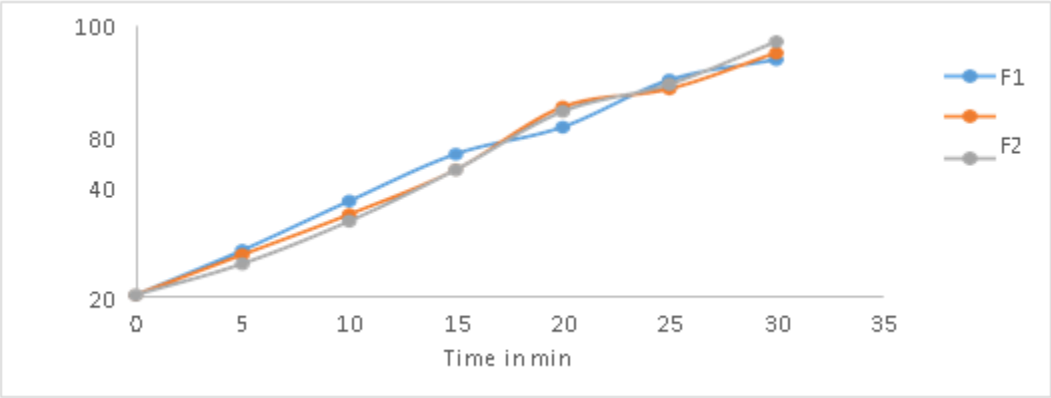

Fig 4 :- In-vitro drug release studies of Repaglinide FDTs of F1, F2 and F3

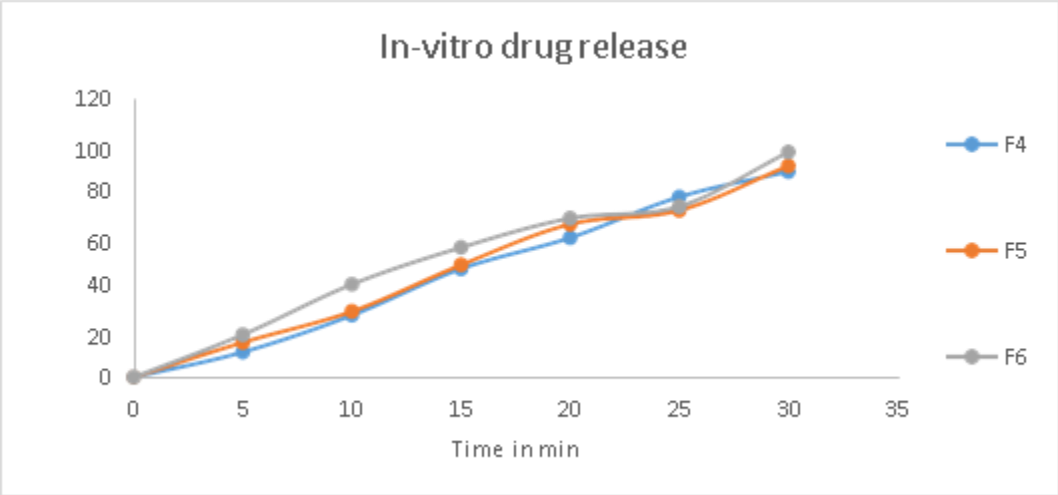

Fig 5: Comparative drug release profile of FDT's formulations of F4, F5 and F6

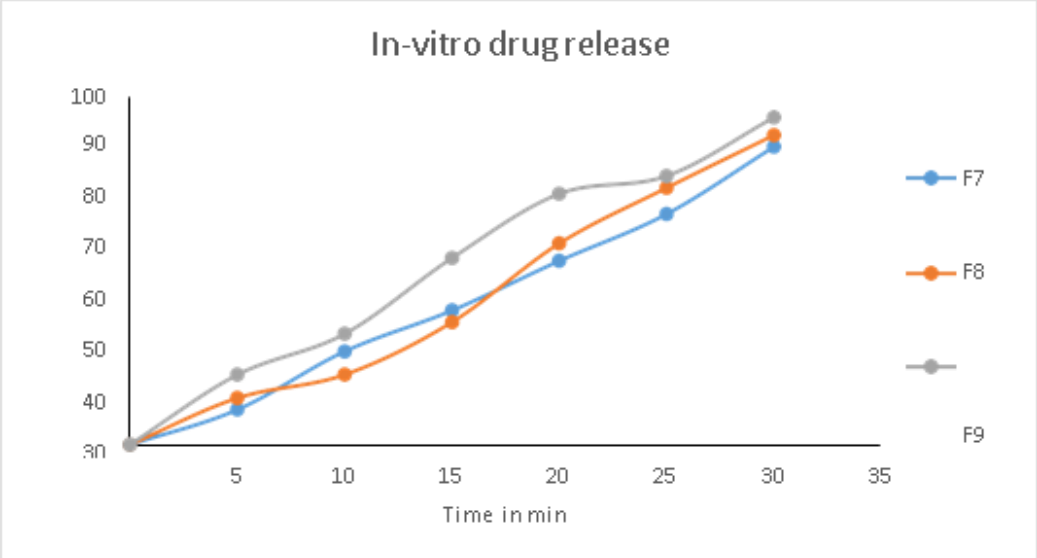

Fig 6: Comparative drug release profile of FDT's formulations of F7, F8 and F9

***In-vitro* drug release studies**

All the formulations were evaluated for their *in-vitro* drug release according to the procedure described in methodology and the. The maximum drug release of 95.26 % was obtained from formulation F6, and minimum drug release of 77.04 % shown by F1. The average drug release immediately after dispersion for all the formulation was in the range of 77.04 % to 95.26 %. The formulation F6 containing Fenugreek Seed Mucilage and enhanced the dissolution rate.

Conclusion:

In present study an attempt was made to design fast dissolving tablets of Repaglinide by direct compression method. Nine formulations were designed by varying the concentration of polymers. All the formulations were evaluated for hardness, thickness, friability, weight variation and drug content estimation, surface pH determination, *in-vitro* drug release and short-term stability study.

FTIR studies revealed no interaction between the drug and excipients. The prepared formulation was evaluated for pre compression and post compression parameters which revealed good flow properties of blends and physical attributes of the prepared tablets were found to be practically within the limits.

Formulation (F1, 2, 4, 5, 7, 8 and F9) passes both pre and post formulation test but failed in disintegration time as it showed more DT and there was no significant increase in the release of drug as increasing the polymer concentration as expected, But formulation F3 and F6 showed less DT compared to other formulation and there was significant increase in the release of drug as increasing the polymer concentration, therefore formulation F3 and F6 were selected as best formulation compared to other formulation were as F6 showed the maximum release of drug 95.26 % CDR in 30 minutes when compare to F3 therefore formulation 6 was selected as the best formulation.

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