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DEVELOPMENT AND *IN-VIVO* EVALUATION OF REPAGLINIDE OSMOTIC DRUG DELIVERY SYSTEM USING TWO DIFFERENT TECHNIQUES

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Abstract:

Objective: *The aim was to formulate elementary osmotic pump (EOP) and push-pull osmotic pump (PPOP) based drug delivery system for controlled release of an anti-diabetic agent, repaglinide.*

Method: *Repaglinide tablets were prepared by EOP and PPOP method by wet granulation technique. 15 formulations F1-F15 were designed by EOP and 14 formulations were done by PPOP method. All the formulations were evaluated for various physicochemical parameters and in-vitro dissolution studies. Further the optimised formulations from both the method were characterized by FTIR, stability studies and pharmacokinetic studies.*

Results*: Repaglinide osmotic tablets were prepared by EOP and PPOP method and exhibited satisfactory results for all evaluated parameters. The highest drug release was exhibited from F15 prepared by EOP method with 99.76% and FF14 with 15% coating prepared by PPOP method with drug release of 99.73%. The study by FTIR indicated no significant interactions between drug and excipients. The formulations were stable after 3 months of accelerated stability studies. In-vivo studies in rabbits showed that osmotic tablet of repaglinide (F15) Cmax of 22.56±0.08 ng/ml and the marketed 's Cmax of 30.73±0.063 ng/ml. Both the osmotic tablet formulation and the commercial product had Tmax values of 6.0 ±0.06 and 1.0 ±0.03 hours, respectively. The osmotic tablet formulation had a greater* $AUC_{0\text{-}infinity}$ *(184.21±1.37 ng. h/ml) than the marketed (153.8 ±0.42 ng. h/ml). In comparison to the marketed, the osmotic tablet formulation had a considerably greater AUC0-t ($p<0.05$).*

Conclusion: *The bioavailability and in-vitro dissolution characteristics of the osmotic tablets of repaglinide were significantly improved in comparison to the commercial product.*

Keywords: *Repaglinide, Hyperglycemia, Osmotic drug delivery system, HPLC,* pharmacokinetics

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INTRODUCTION:

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). Conventional drug delivery systems have no control over the drug release and effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations; hence once-daily controlled release preparation is often desirable [1]. Drug release from oral controlled release dosage forms may be affected by pH, gastrointestinal motility, and presence of food in the gastrointestinal tract. One practical approach with a potential to overcome the above said disadvantages is the osmotic drug delivery system, wherein drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis.

The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it by means of a laser beam or mechanical drill [2].

Repaglinide is the first member of the class of oral hypoglycaemics designed to normalize the meal time glucose excursions. It is administered before each major meal to control postprandial hyperglycemia. After oral administration, Repaglinide is rapidly and completely absorbed from the gastrointestinal tract. Its having half-life (0.9-1 hour). The maximum tolerable dose of repaglinide is 16mg per day [3]. In the present investigation, an attempt was made to design a simplified controlled porosity osmotic system of repaglinide and development of sustained release tablet dosage, which is expected to improve patient compliance due to reduced frequency.

MATERIALS:

Repaglinide was gifted from Hetero drugs Ltd, Hyderabad. Fructose, KCl, Mannitol, microcrystalline cellulose(pH101), talc and magnesium stearate, HPMC K4M, Cellulose acetate, PEG400, PEG 6000, Di butyl Pthalate and acetone obtained from Gattefosse, Mumbai. Sodium chloride (NaCl), Polyox WSR N 80, Povidone K30, Butyl hydroxy toulene, stearic acid, Polyox coagulant, Iron Oxide (red), Hydroxy ethyl cellulose, Polyethylene glycol 3350, Cellulose acetate and Propylene Glycol, were purchased from S.D. Fine-Chem Ltd. All the chemicals used were of analytical grade**.** Marketed product (NovoNorm 2 mg) obtained from local market.

METHOD:

Preparation of repaglinide tablets by elementary osmotic pump (EOP) method

Preparation of core tablets

The core osmotic tablets were prepared by direct compression technique and preparation of osmotically controlled tablets, drug was mixed with mannitol, KCl and fructose, as an osmotic agent in different concentration and HPMC K4M is added to it and mixed. Avicel PH 101 were sifted together through 40# sieve and blended for 15 minutes. The blend was again passed through 40 # sieve and lubricated with talc and magnesium stearate (previously Sifted through 60 # sieve) for 5 minutes. The blend was compressed into tablets using multi station rotary tablet punching machine (Cadmach, Ahmedabad, India) of keeping round standard concave punch. Formulation composition are shown in Table 1.

Table 1: Composition of core tablet

Ingredients	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15
Repaglinide	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	10	20	30	40	50	0	0	0	0	0	5	10	15	20	25
Fructose	5	10	15	20	25	10	20	30	40	50	0	0	0	0	0
Potassium chloride	0	0	0	0	0	5	10	15	20	25	10	20	30	40	50
HPMC K4M	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Avicel PH 101	90	75	60	45	30	90	75	60	45	30	90	75	60	45	30
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg.stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total Wt.	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**	**124**

Coating of tablets

A coating of cellulose acetate as a semi permeable membrane was done around the tablets in which PEG 400 and PEG 6000 are added in 20 %(w/w) Concentration of cellulose acetate as pore forming agent & dibutyl pthalate was added at 10%(w/w) concentration of cellulose acetate to achieve proper plasticity. Then required quantity of acetone and methanol was gradually mixed with the resultant polymeric solution for 80-100 RPM using Remi magnetic stirrer coating was performed by painter spray Gun PS-3(Sheffield, United Kingdom) in a Manesty 354255 Coating pan (Bosch, Germany). Coating process was started with rotation speed of 4 to 5 rpm. The spray rate and atomizing air pressure were 4 to 6 ml/min and 17.5 kg/cm2, respectively Inlet and outlet air temperatures were 60°C±10°C and 45°C, respectively. Coated tablets were dried at 50°C for 12 hours and the percentage weight gain of the coating membrane was measured. The detailed composition is mentioned in coating solution composition table 2 [4,5].

Table 2: Composition of coating solution

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Cellulose Acetate (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
PEG 400 %(w/w)	20	20	20	0	0	0	0	0	0	0	0	0	0	0	0
PEG 6000 %(w/w)	-	-		20	20	20	20	20	20	20	20	20	20	20	20
Di butyl Pthalate %(w/w)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Weight Gain (%)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total weight after coating	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2	130.2

Evaluation tests

Pre-compression parameters

Post compression evaluation tests [6-8]

Post compression evaluation tests like weight variations, thickness, hardness, friability were recorded as per the procedure given in reference.

Content uniformity

Assay was performed as per given reference and drug content analyzed spectrophotometrically in UV spectrophotometer at 258 nm [9].

***In vitro* drug release studies**

The dissolution study of tablets was conducted using dissolution testing USP apparatus II (paddle method) in 900ml of pH-6.8 phosphate buffer was placed in the vessel and assembled. The medium was allowed to equilibrate to temperature of 37±0.5°C. A tablet was placed in the vessel and covered; the apparatus was operated up to 24 h at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium. Suitable dilutions were done with dissolution medium and were analysed spectrophotometrically at λ_{max} of 258 nm using a UV-spectrophotometer [10].

Stability studies

Prepared repaglinide coated tablets were placed under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75% ± 5% RH and temperature of 40°C ± 2°C for accelerated stability studies as mentioned in ICH guidelines. Samples were removed after 1, 2, and 3 months and evaluated. [11]

Characterization of repaglinide EOP tablets

FTIR

FT-IR spectra were recorded on samples in potassium bromide disks using shimadzu FTIR 8400S spectrophotometer. Sample was prepared in

potassium bromide disks by means of a hydrostatic pallet press (type KP 919). The scanning range was 250-4500 Cm^{-1} and the resolution was 4 cm [12].

Preparation of repaglinide tablets by push pull osmotic pump (PPOP) method

Formulation development

The formulation of core tablets was consisted of drug layer of repaglinide, Povidone K30, polyethylene oxide & stearic acid and Push layer of polyethylene oxide, sodium chloride, stearic acid and ferric oxide red. Active pharmaceutical ingredient (API) and all the excipients were passed through 40-mesh sieve before use, respectively. The drug layer blend was prepared by mixing repaglinide and other excipients in blender (white layer). The push layer blend was prepared by mixing all push layer excipients in blender (red color layer). Core tablets were compressed by a bilayer tablet machine (Eliza Press EP-400) equipped with a particular standard concave punch (7 mm diameter) (ACG Palm, India). The compress process was as follows: Firstly, drug layer follows push layer of red color get compress with hardness range of final tablet 7-9 kilo pascals. Compressed tablets continue for sub coating and follows enteric coating in optimization approach (table 3). [13,14]

Table 3: Formulation table of core tablet

Ingredients	PP1	PP2	PP3	PP4	PP5	PP6	PP7	PP8	PP9	PP10	PP11	PP12	PP13	PP14
Drug Layer														
Drug	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Polyox WSR N 80	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4	82.4
Povidone K30	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Butyl hydroxy toulene	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
stearic acid	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**
Push Layer														
Polyox coagulant	40	30	20	10	0	0	0	0	0	0	0	0	0	0
Polyox WSR 300	0	10	20	30	40	40	40	40	40	40	40	40	40	40
NaCl	40	40	40	40	40	40	40	40	40	40	40	40	40	40
stearic acid	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Iron Oxide (red)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total weight (core)	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**

Coating of bilayer tablets

Sub-caoting suspension prepared by adding hydroxy ethyl cellulose (HEC) & polyethylene glycol in purified water under stirring. Sub-coating builds up carried for 3-8% of core tablet weight and optimized for further enteric coating process. Enteric coating suspension prepared by adding of cellulose acetate (CA) & polyethylene glycol in Acetone and purified water (95:5) under stirring. Enteric coating builds up carried for 6-15% of sub-coat tablet weight and optimized the formulation. Coating process (both sub coating & enteric coating) carried by a traditional coating pan (GanscoaterGAC-250) For sub-coating maintain bed temperature at about 38～420 C, rotating rate of the pan was 5～8 rpm, spraying rate was 5ml/min. For enteric coating maintain bed temperature at about 22～270 C, rotating rate of the pan was 5～8 rpm, spraying rate was 15 ml/min. Under this circumstance, the core tablets & sub-coated tablets were sprayed and covered a homogeneous coating membrane of dissimilar material, respectively. To clear away the residual solvent and aging the membrane, the coating tablets were dried for 1 h at 40ºC in the coating pan for each coating in inching mode (table 4). [14,15]

Table 4: Formulation table of coated tablet

Formulation code	**FF1**	**FF2**	**FF3**	**FF4**	**FF5**	**FF6**	**FF7**	**FF8**	**FF9**	**FF10**	**FF11**	**FF12**	**FF13**	**FF14**
Sub coating %	**4**	**4**	**4**	**4**	**3**	**4**	**5**	**6**	**7**	**8**	**4**	**4**	**4**	**4**
Hydroxy ethyl cellulose	6	6	6	6	5	6	8	10	11	13	6	6	6	6
Polyethylene glycol 3350	0.848	0.848	0.848	0.848	0.136	0.848	0.56	0.272	0.984	0.696	0.848	0.848	0.848	0.848
purified water	Qs	Qs	qs	qs	Qs	qs	qs	qs	qs	qs	qs	qs	qs	Qs
Total weight (Subcoated)	**178.048**	**178.048**	**178.048**	**178.048**	**176.336**	**178.048**	**179.76**	**181.472**	**183.184**	**184.896**	**178.048**	**178.048**	**178.048**	**178.048**
Final coating														
Cellulose acetate	17	17	17	17	18	17	15	13	12	10	20	22	24	26
Propylene Glycol	0.8048	0.8048	0.8048	0.8048	1.5168	0.8048	1.0928	1.3808	0.6688	0.9568	1.365	1.146	0.926	0.7072
Wt. Gain	10%	10%	10%	10%	11%	10%	9%	8%	7%	6%	12%	13%	14%	15%
total weight after coating	**195.853**	**195.853**	**195.853**	**195.853**	**195.853**	**195.853**	**195.853**	**195.853**	**195.853**	**195.853**	**199.413**	**201.194**	**202.974**	**204.755**

Drilling of Bilayer Tablets: The bilayer coated tablets were drilled by Cameron microdrill press

Evaluation of repaglinide PPOP tablets

Physical properties

Average weight, Hardness, Thickness, friability were recorded

%Drug Content:

As per preferred method under EOP.

***In vitro* Release of repaglinide PPOP tablets**

As per referred methods under EOP

Effect of Agitation Intensity: In order to assess the effect of the agitational intensity of the release media, the release studies of the optimized formulation were carried out in a dissolution rate test apparatus II at various rotational speeds. The paddle rotation speed was adjusted at rates of 50,75and100 rpm. The samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45µm nylon membrane filters.

Drug release kinetics of repaglinide PPOP tablets

As per preferred method under EOP.

Stability studies

Prepared repaglinide coated tablets were placed under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75% ± 5% RH and temperature of 40°C ± 2°C for accelerated stability studies as mentioned in ICH guidelines. Samples were removed after 1, 2 and 3 months and evaluated.

Characterization of repaglinide PPOP tablets

The optimized tablet formulation analyzed for FTIR as per the referred methods under EOP method.

Pharmacokinetic studies of Repaglinide in rabbit plasma

Animal preparation

Eighteen albino male rabbits were (weighing 2–3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25°C, RH 45%, and 12 h alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. An in vivo pharmacokinetic study was conducted in accordance with the ethical guidelines for investigations in laboratory animals and approved by the Institutional Animal Ethics Committee [15]

Study design

Three groups (Group A, B, and C) each containing six rabbits were created at random. Using a Ryle's tube with a diameter of 4 mm, the rabbits in Group A were given minitablets of repaglinide's optimised osmotic tablet formulation, while the rabbits in Group B were given the commercially available reference product (NovoNorm 2mg) triturated and diluted with carboxymethylcellulose sodium (CMC-Na) at a dose corresponding to their body weight. [16]

Blood sampling

Blood samples (approximately 0.5 ml) were obtained with syringes by marginal ear vein at regular intervals 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 h post doses. During collection, blood sample has been mixed thoroughly with heparin to prevent blood clotting. Plasma was separated by centrifugation of the blood at 7500 rpm in cooling centrifuge for 20 min and stored frozen at −20°C until analysis. 20 µL of supernatant was collected by micro syringe and directly injected into HPLC column.

Determination of Repaglinide in Rabbit plasma by HPLC method

Chromatographic conditions [17]

The Shimadzu HPLC system in Kyoto, Japan, comprises of a binary pump (LC-20AD), a UV/Visible detector (SPD-A20), a Rheodyne injector port (7725i), and a 20 l loop volume. Data acquisition was carried out using LC-solutions software. Materials were weighed using a 0.1 mg precision balance (Denver Instruments, New York). Vortex mixer, chilled centrifuge, and deep freezer were used in the processing of plasma samples (Remi, India)

The chromatograms were created on an analytical column C18 (2), 250 mm x 4.6 mm x 5 microns (Luna®, Phenomenex) using isocratic elution with a fixed composition of ACN:

A continuous flow rate of 1 ml/min was used to pump 0.05% TFA in water (55:45, v/v) mixture, and 285 nm was used as the detection wavelength throughout the entire investigation. Prior to each batch analysis, the eluent's composition was freshly combined for the needed volume, passed through a membrane filter (#0.45 m), and degassed using an ultrasonic bath.

Preparation of solutions

To prevent analyte breakdown during storage, individual primary stock solutions of repaglinide (REP) and internal standard (IS) rabeprazole (RAB) (1 mg/ml) were made using methanol as the solvent and stored at a cold temperature. Working standards (WS) at concentrations of 0.1, 0.25, 0.5, 1, 2.5, 5 and 10 g/ml were prepared by properly diluting the primary stock solution of REP with a mobile phase mixture. A single WS solution of IS (5 g/ml) was also prepared for the whole study. Prior to analysis, the standards for calibration (CS) were created by spiking individual rabbit plasma samples (180 l) with each WS solution of REP (20 l) to produce plasma-drug mixtures with concentrations of (10, 25, 50, 100, 250, 500, and 1000 ng/ml). The lower limit of quantitation (LLOQ), low quality control (LQC; 3*LLOQ), medium quality control (MQC; 50% of upper LOQ), and high quality control (HQC; 90% of upper LOQ) standards for REP were independently made at concentration levels of 10 ng/ml, 30 ng/ml, 500 ng/ml, and 900 ng/ml, respectively, as described in the CS method.

A good separation of repaglinide and internal standard (rabeprazole) were achieved with the retention times of 4.4 and 5.5 min respectively without interference of endogenous compounds in rabbit plasma. Each sample was subjected three times and the same retention times were observed in all the cases. In addition, the total run time for each injection per sample was only 10 min.

RESULT AND DISCUSSION:

Physicochemical properties

The value of hardness, weight variation of prepared core and coated tablets were found to be satisfactory

The **drug content** of all formulation is in between 95.35-99.63%, drug content with highest exhibited by F15 formulation.

***In vitro* dissolution study**

Figure 1shows that without coating (P1 - P15) none of the batch give controlled release and release of drug limited to16 h only which are not meeting the objectives and all the batches shows good and satisfactory release data and selected for the next step for coating them. In porous osmotic pump tablet the drug release rate is depends on the concentration of

osmotic agent and pore former used. The osmotic agent concentration increases then osmotic pressure created inside the tablet also increase; the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drugs the release of the drug also will increase. The poreformer is added here in coating solution so, it will cause easy leaching out of the drug from the formulation. Here the mechanical drilling was done for orifice formation after drying of the coating layer. So here the dual concepts of EOP as well as microporous were used in for release of the drug from tablets. (F1- F15) shows that all 15 batches are showing release upto 24h and in that F15 is optimized with release of 99.76% release profile as shown in figure 2.

FTIR studies

The FTIR spectra of pure repaglinide showed the main characteristic peaks of amine are NH at 3500-3300 cm^{-1}, -NH at 1660-1520 $cm^{-1}$and –C-H at 1350-1010 cm^{-1} The –C-N peaks of fatty amine can belocated around 1260-1030 cm^{-1}, while the -OH and –C-O peaks of alcoholic hydroxyl group can be found at 3400-3100 cm^{-1}, and wide stretch at 1270-1000 cm^{-1}. The FTIR spectrum of repaglinide with HPMC K4M showed similar peaks at 3500-3400 cm-1 which indicated OH vibrational stretching, the band between 1650 and 1600 cm-1 indicated the presence of stretching vibration of -C-O for six membered cyclic rings, the band at 1100-1000 cm-1 was for stretching vibration of ethereal C-O-C groups. This confirms that all the peaks major peaks present in marketed repaglinide also present in optimised formulation F14 suggesting no significant interaction observed between them. (Fig 3 and 4).

Stability studies

Optimized formulation (F15) was subjected to stability study for 90 days at accelerated as per ICH guidelines. The optimized formulation was stable during 3 months period. Results indicate that optimized formulation (F15) is stable with no variations in its physical properties (table 5).

Table 5: Stability studies of F15 stored at 40 ±2^{0}C /75±5% RH

Retest Time for Optimized formulation F15	Drug content (%)	*In-vitro* drug release profile (%)	Hardness (kg/cm^2)
0 days	99.63±0.69	98.64±1.46	5.32±0.35
30 days	99.12±1.34	98.26±1.21	5.32±0.36
60 days	98.77±0.53	97.97±0.25	5.32±1.15
90 days	98.07±1.26	97.18±1.75	5.33±1.68

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Table 6: Stability studies of FF14 stored at 40 ±2^{0}C /75±5% RH

Retest Time for Optimized formulation F14	Drug content (%)	*In-vitro* drug release profile (%)	Hardness (kg/cm^2)
0 days	99.26±0.27	99.73±1.58	4.4±0.56
30 days	98.74±0.38	99.36±0.26	4.4±0.38
60 days	98.39±0.37	99.01±0.25	4.4±0.77
90 days	98.03±0.72	98.73±0.28	4.4±0.27

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Table 7: Pharmacokinetic Parameters of Repaglinide osmotic tablet formulation and marketed reference in rabbit plasma

Pharmacokinetic parameters	Repaglinide marketed reference	Repaglinide– osmotic tablet Optimized Formulation
C $_{max}$ (ng/ml)	30.73±0.063	22.56±0.08
AUC $_{0-t}$ (ng. h/ml)	138.425±1.04	164.42±1.74
AUC $_{0-inf}$ (ng. h/ml)	153.8±0.42	184.21±1.37
T $_{max}$ (h)	1.0±0.03	6.0±0.06
t $_{1/2}$ (h)	2.97±0.02	5.67±0.04

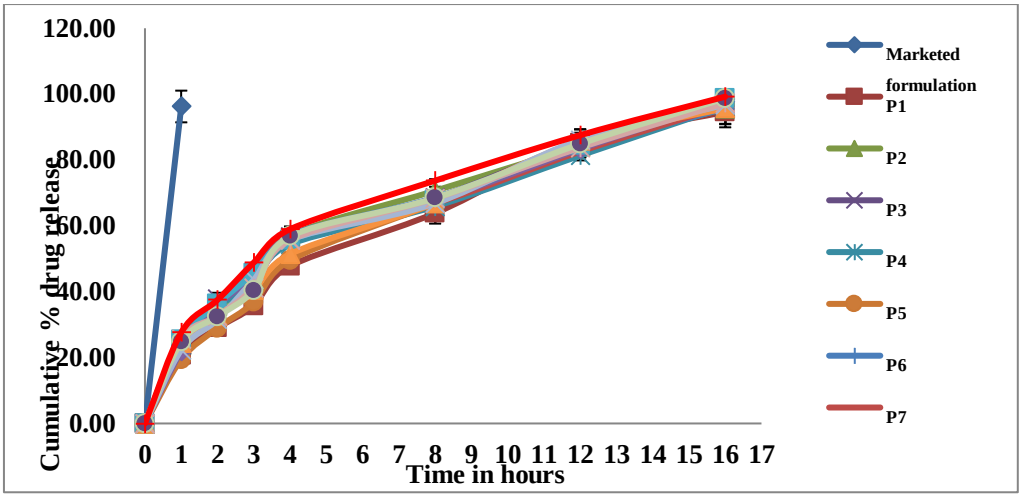

Figure 1: Cumulative percentage drug release of repaglinide marketed formulation and repaglinide EOP core tablets (P1-P15)

RESULTS

Physicochemical properties

The value of hardness, weight variation of prepared core and coated tablet were found to be satisfactory.

The **drug content** of all formulation is in between 94.73-99.26%, drug content with highest exhibited by F14 formulation and depends on angle of repose because if the angle of repose is excellent then drug content is also uniform and the flow property is good hence the drug is evenly distributed in the formulation.

In-vitro drug release

In-vitro drug release study was performed for all batches (FF1-FF14) and found that dissolution profile was dependent mainly on the polymer Polyox WSR 300 (40 mg/Tablet), sub coating optimum percentage build-up (i.e., 4%) and enteric coating optimum percentage build-up (i.e. 15%). As the concentration of sub coating was varied from above or below 4% the drug release was fast and only sustained for 20hours as observed in FF5, FF7, FF8, FF9 and FF10 and as the enteric coating was increased from 6-15% the results were showing best with increase in drug release and with controlled drug release up to 24hours which is observed in FF11-FF14 where the enteric coating was increased from 12-15% the drug release was increased from 96.72% to 99.73%. Hence the concentration of polymer, sub coating and enteric coating are considered as the key formulation optimized parameters (fig 5)

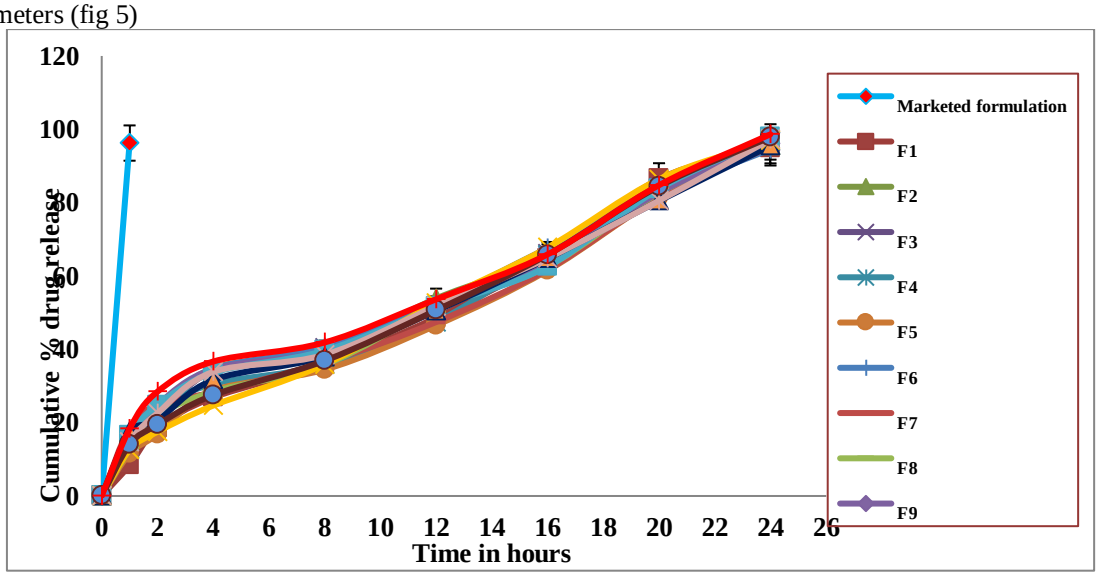

Figure 2: Cumulative percentage drug release of repaglinide marketed formulation and repaglinide EOP coated tablets (F1-F15)

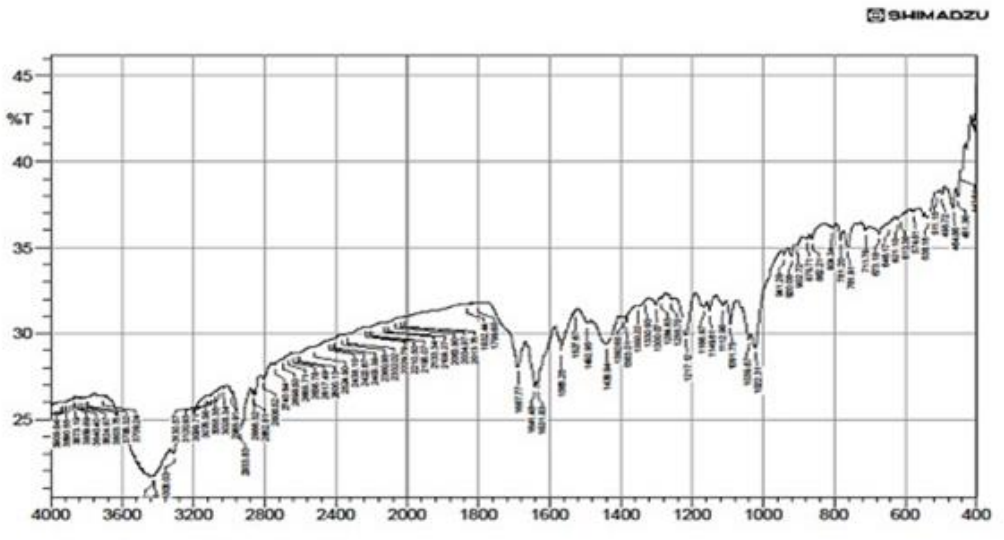

Figure 3: FTIR Spectra of marketed

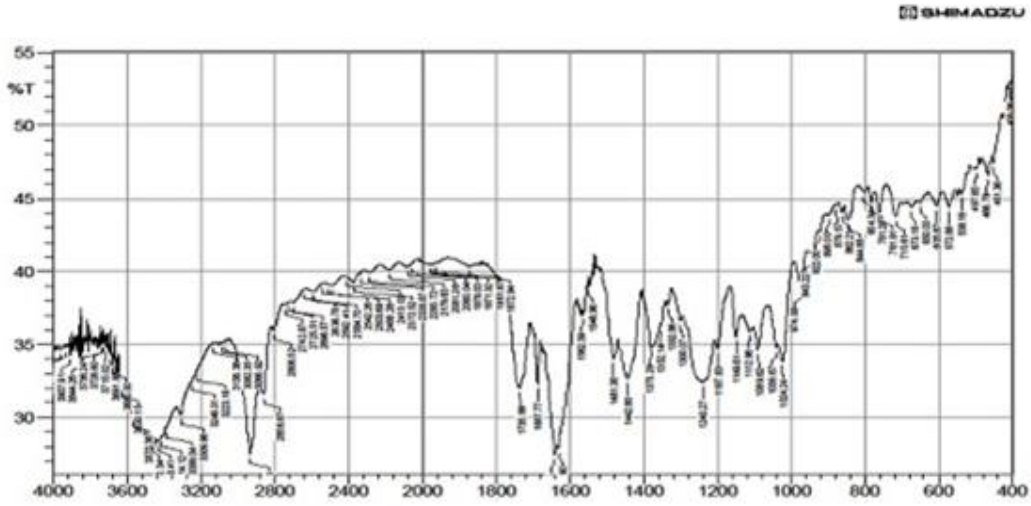

Figure 4: FTIR Spectra of repaglinide optimized formulation (F15)

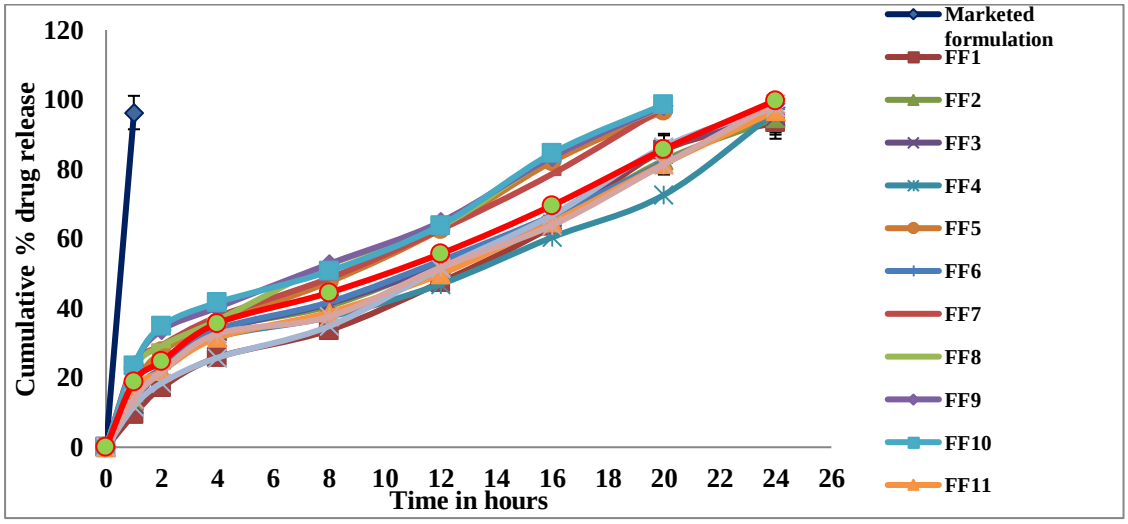

Figure 5: Cumulative percentage drug release of repaglinide marketed formulation and repaglinide PPOP tablets (FF1-FF14)

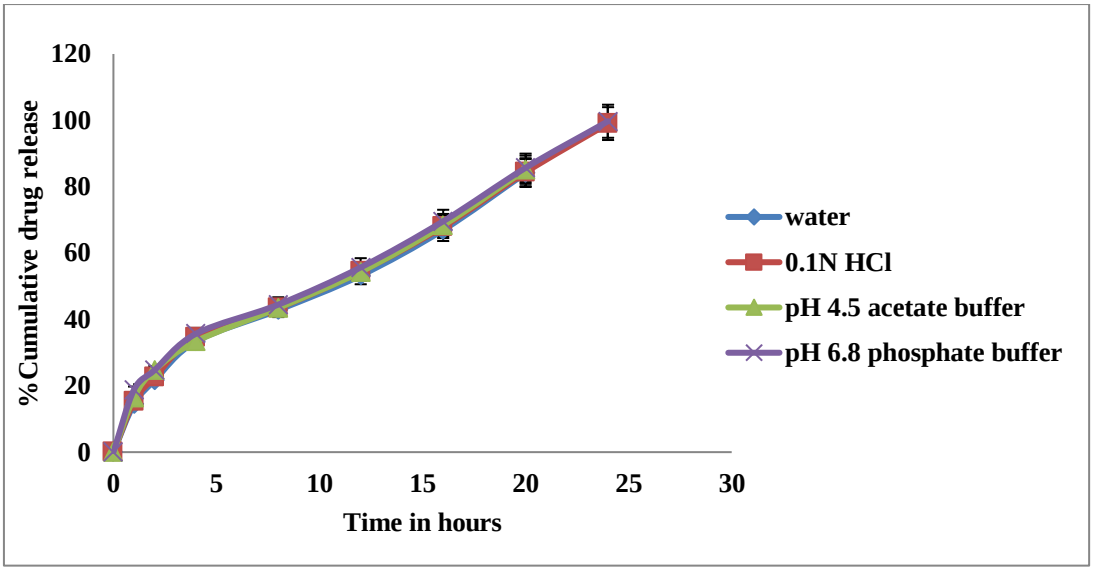

Figure 6: Effect of pH on PPOP optimized formulation FF14

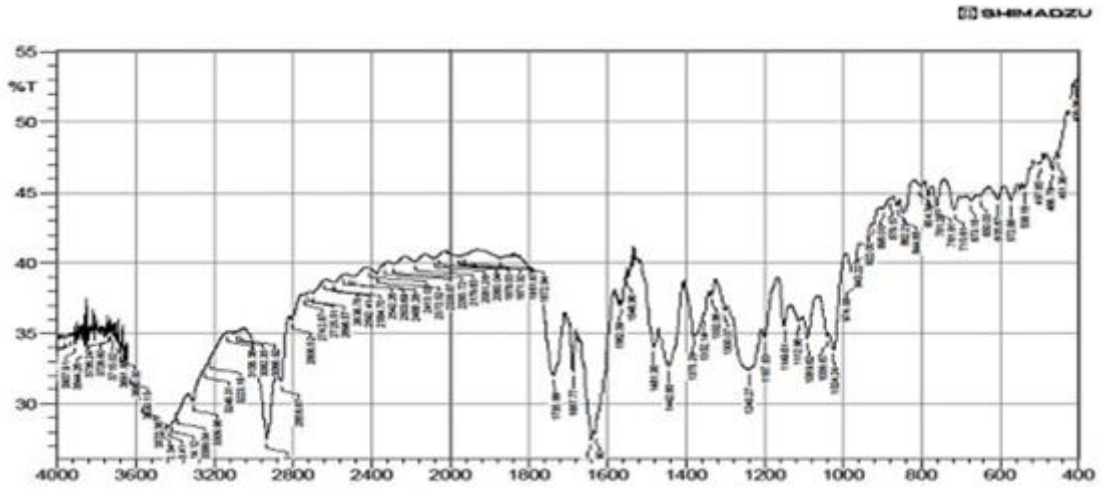

Figure 7: FTIR Spectra of repaglinide optimized formulation FF1

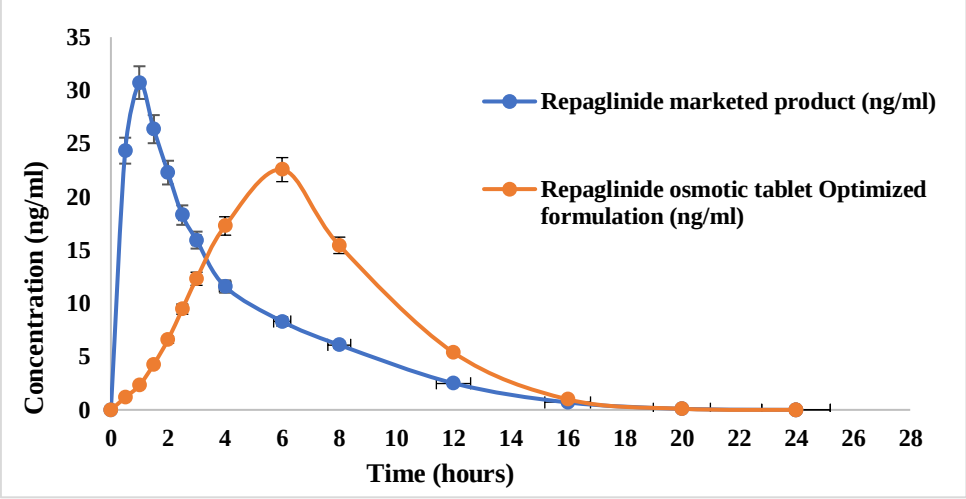

Figure 8: Plasma concentration profiles of Repaglinide osmotic tablet and marketed reference in rabbit plasma

Characterization of PPOP optimized formulation FF14

Effect of pH: When formulation FF14 was subjected to in vitro release studies in buffers of differing pH and in distilled water, no significant difference in release profiles was observed. In other words, the developed push-pull osmotic tablet was found to exhibit Ph independent release kinetics (figure 6).

Effect of Agitation Intensity: The effect of different agitation rate on formulation FF14 was also studied at 50,75 and 100 rpm. There was no significant change in the drug release rate was observed. Hence, it can be concluded that the release rate of push-pull osmotic tablet was independent of agitational intensity.

FTIR studies

The FTIR spectra of pure repaglinide showed under EOP method (fig 3). The FTIR spectrum of repaglinide with povidone K30 and NaCl showed all the peaks for repaglinide suggesting no significant interaction observed between them (fig 7).

Stability studies

Optimized formulation (FF14) was subjected to stability study for 90 days at accelerated as per ICH guidelines. The optimized formulation was stable during 3 months period. Results indicate that optimized formulation (FF14) is stable with no variations in its physical properties (table 6).

Pharmacokinetic data of repaglinide marketed product and optimised repaglinide osmotic tablet F15

Repaglinide concentrations in plasma following oral administration of repaglinide marketed reference and optimized repaglinide osmotic tablet administered oral route are given in Table **7** and respective plasma concentration-time curves are shown in Figure 8

C_{max} of the osmotic tablet 22.56±0.08ng/ml was significant ($p<0.05$) as compared to the repaglinide marketed reference formulation 30.73±0.063 ng/ml. T_{max} of both osmotic tablet formulation and repaglinide marketed reference was 6.0±0.06h and 1.0±0.03h, respectively. $AUC_{0-\infty}$ infinity for osmotic tablet formulation was higher (184.21±1.37 ng.h/ml) than the repaglinide marketed reference formulation 153.8±0.42 ng.h/ml. Statistically, AUC_{0-t} of the osmotic tablet formulation was significantly higher ($p<0.05$) as compared to repaglinide marketed reference formulation. Higher amount of drug concentration in blood indicated better systemic absorption of Repaglinide from osmotic tablet formulation when compared to the repaglinide marketed reference and also in vivo pharmacokinetic studies in rabbits confirmed the prolonged release by showing increase in bioavailability for Repaglinide from osmotic tablet formulation as compared to the repaglinide marketed reference formulation.

CONCLUSION:

Repaglinide osmotic tablets were prepared successfully by EOP and PPOP methods. In EOP method the drug release was mainly depending upon osmogen in core and pore forming agent in coating, formulation F14 with high osmogen and pore forming agent concentration exhibited highest drug release of 99.76% for 24h was optimised. In PPOP method the formulation FF14 with highest concentration of coating showed highest drug release of 99.73% for 24h was optimised. Hence, it was revealed that the F15 and FF14 were optimized formulations that was used for further studies and evaluation. FTIR studies indicated insignificant interaction and found to be stable after 3 months. The repaglinide optimised osmotic tablet' F15 formulation C_{max} of 22.56±0.08 ng/ml and the marketed's C_{max} of 30.73±0.063 ng/ml. Both the osmotic tablet formulation and the marketed had T_{max} of 6.0±0.06 and 1.0±0.03 hours, respectively. The osmotic tablet formulation had a higher $AUC_{0\text{-infinity}}$ (184.21±1.37 ng. h/ml) than the marketed (153.8±0.42 ng. h/ml). In comparison to the marketed, higher drug concentrations in the blood showed better systemic absorption of Repaglinide from osmotic tablet formulation.

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