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Research Article

Optimization of Repaglinide Osmotic Drug Delivery System Using Two Different Techniques

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ABSTRACT

The current study aimed to formulate an elementary osmotic pump (EOP) and push-pull osmotic pump (PPOP) based drug delivery system for controlled release of an anti-diabetic agent, repaglinide is expected to provide sustained release. EOP and PPOP method prepared repaglinide tablets by wet granulation technique. EOP designed 15 formulations F1-F15 and 14 formulations were done by PPOP method. All the formulations were evaluated for various physicochemical parameters and in-vitro dissolution studies. The release data was fitted into mathematical kinetic modeling studies to check the release mechanism. Further, the optimized formulations from both methods were characterized by FTIR and stability studies. EOP and PPOP methods successfully prepared repaglinide osmotic tablets. All the formulations 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%. Based on the *in vitro* dissolution profile, formulation F15 and FF14 exhibited zero-order with Korsmeyer-Peppas kinetics with Fickian diffusion-controlled release mechanism with high drug release in 24 hours and hence were selected as optimized formulations. The drug-excipient compatibility study by FTIR indicated no significant interactions between drugs and excipients. The formulations were stable after 3 months of accelerated stability studies. EOP and PPOP were designed to effectively administrate repaglinide drugs for a prolonged period of time.

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 the presence of food in the gastrointestinal tract. One practical approach with the 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 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 mealtime glucose excursions. It is administered before each major meal to control postprandial hyperglycemia. After oral administration, repaginate is rapidly and completely absorbed from the gastrointestinal tract. The half-life is 0.9-1 hour. The maximum tolerable dose of repaglinide is 16mg per day.^[3] In the present investigation, an attempt

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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.

MATERIAL AND METHODS

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, dibutyl phthalate, and acetone were obtained from Gattefosse, Mumbai. Sodium chloride (NaCl), polyox WSR N 80, povidone K30, butylhydroxytoluene, stearic acid, polyox coagulant, iron oxide (red), hydroxyethylcellulose, 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 a local market.

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. The drug was mixed with mannitol, KCl, and fructose, as an osmotic agent in different concentrations, and HPMC K4M was added to it and mixed. Avicel PH 101 was 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 a multi-station rotary tablet punching machine (Cadmach, Ahmedabad, India) to keep round standard concave punch. Formulation compositions are shown in Table 1.

Coating of Tablets

A coating of cellulose acetate as a semipermeable 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 phthalate 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). The coating process was started with a 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, Inlet and outlet air temperatures were 60 ± 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]

Evaluation Tests

Pre-compression Parameters

The lubricated blend was evaluated for angle of repose, bulk density, tapped density, Carr's index, and Hausner's Ratio as per referred procedures.^[5]

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

Table 2: Composition of a 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
Dibutyl phthalate %(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



Post Compression Evaluation Tests^[6-8]

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

Content Uniformity

The assay was performed as per the given reference, and drug content was 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 a temperature of $37 \pm 0.5^\circ\text{C}$. A tablet was placed in the vessel and covered; the apparatus was operated up to 24 hours at 50 rpm. At a definite time interval, 5 mL of dissolution medium was withdrawn, filtered, and replaced with 5 mL of fresh medium. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} of 258 nm using a UV-spectrophotometer.^[10]

Drug Release Kinetics

To elucidate the mode and mechanism of drug release, the data from the in-vitro release study were fitted into various kinetic models such as zero-order, first-order, Higuchi's, and Korsmeyer-Peppas model.^[11]

Stability Studies

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

Characterization of Repaglinide EOP Tablets

FAIR

FT-IR spectra were recorded on samples in potassium bromide disks using Shimadzu FTIR 8400S spectrophotometer. The sample was prepared in potassium bromide disks by means of a hydrostatic pallet press (type KP 919). The scanning range was $250-4500\text{ cm}^{-1}$, and the resolution was 4 cm^{-1} .^[12]

Preparation of Repaglinide Tablets by Push-Pull Osmotic Pump (PPOP) Method

Formulation Development

The formulation of core tablets consisted of a drug layer of repaglinide, povidone K30, polyethylene oxide, and stearic acid, and a push layer of polyethylene oxide, sodium chloride, stearic acid, and ferric oxide red. Active pharmaceutical ingredient (API) and all the excipients were passed through a 40-mesh sieve before use, respectively. The drug layer blend was prepared by mixing repaglinide and other excipients in a blender (white layer). The push layer blend was prepared by mixing all push layer excipients in a 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 compressing process was as follows: Firstly, the drug layer follows a push layer of red color gets compressed with a hardness range of final tablet 7-9 kilopascals. Compressed tablets continue for sub-coating and follow enteric coating in the optimization approach (Table 3).^[13,14]

Coating of Bilayer Tablets

Sub-coating suspension prepared by adding hydroxyl ethyl cellulose (HEC) and polyethylene glycol in purified water under stirring. Sub-coating builds up carried for

Table 3: Formulation table of core tablet

Ingredients	PP1	PP2	PP3	PP4	PP5	PP6	PP7	PP8	PP9	PP10	PP11	PP12	PP13	PP14
<i>Drug layer</i>														
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 toluene	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
<i>Push Layer</i>														
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

3-8% of core tablet weight and optimized further enteric coating. Enteric coating suspension is prepared by adding cellulose acetate (CA) and polyethylene glycol in acetone and purified water (95:5). Enteric coating built up 6-15% of sub-coat tablet weight and optimized the formulation. The coating process (both sub coating and enteric coating) carried by a traditional coating pan (GanscoaterGAC-250) for sub-coating maintains bed temperature at about 38~42°C, rotating rate of the pan was 5~8 rpm, spraying rate was 5ml/min. For enteric coating, maintain bed temperature at about 22~27°C, rotating rate of the pan was 5~8 rpm, spraying rate was 15 mL/min. Under this circumstance, the core tablets and 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-hour at 40°C in the coating pan for each coating in inching mode (Table 4).^[14,15]

Drilling of Bilayer Tablets

The bilayer coated tablets were drilled by Cameron microdrill press.

Evaluation of Repaglinide PPOP Tablets

Pre-compression Parameters

Weight variation, hardness, thickness, and friability were recorded per the referred procedures mentioned in the EOP method.

Physical Properties

Average weight, hardness, thickness, friability were recorded.

% Drug Content

As per the preferred method under EOP.

In Vitro Release of Repaglinide PPOP Tablets

As per referred methods under EOP

Effect of Agitation Intensity

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 50, 75, and 100 rpm rates. The samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45 µm nylon membrane filters.

Drug Release Kinetics of Repaglinide PPOP Tablets

As per preferred method under EOP.

Characterization of Repaglinide PPOP Tablets

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

Stability Studies

Prepared repaglinide-coated tablets were placed under a controlled temperature environment inside a stability

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
Hydroxyethylcellulose	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
<i>Final coating</i>														
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



chamber (Thermo Lab, India) with a relative humidity of $75\% \pm 5\%$ RH and temperature of $40 \pm 2^\circ\text{C}$ for accelerated stability studies as mentioned in ICH guidelines. Samples were removed after 1, 2, and 3 months and evaluated.

RESULTS AND DISCUSSION

Micromeritic Properties of Repaglinide Granules For EOP Tablets

Granules prepared for compression of repaglinide EOP tablets were evaluated for their flow properties.

The bulk densities of all the formulations P1 to P15 were measured, and they are ranged from $0.44 \pm 0.54\text{g/cc}^3$ to $0.53 \pm 0.62\text{g/cc}^3$.

The tapped density of all the formulations P1 to P15 was measured, and they are ranged from $0.42 \pm 0.96\text{g/cc}^3$ to $0.52 \pm 0.42\text{g/cc}^3$.

The angle of repose of all the formulations was found to be good. The formulation P15 was 25.57 ± 0.52 , having excellent flow properties.

The compressibility index values were found to be in the range of 7 to 14%, and carrs index values ranged between 1.10 ± 0.73 to 1.17 ± 0.39 . These findings indicated that all the batches of formulations exhibited good flow properties.

Physicochemical Properties

The value of hardness weight variation of a prepared core tablet is recorded. The hardness, friability, weight variation, uniformity of content of the prepared coated tablet is recorded. Here tablets before coating were coded as P1-P15 and as F1-F15 after coating. The results for weight variation of core tablets passed the test and were within limits.

The weight variation of all the coated formulations is within limits; adequate tablet hardness is necessary for consumer acceptance and handling.

The measured hardness of each batch of all formulations tablets, i.e., F1 to F15, ranged between 5.32 to 5.89 Kg/cm^2 .

The thickness of the tablets was found to be almost uniform in all formulations F1 to F15.

The thickness of all the formulations ranged between 1.8 - 2.2 mm .

The friability of all prepared formulations is between 0.16 to 0.22 . The friability properties limits are between 0 - 1% .

The drug content of all formulations is between 95.35 - 99.63% , drug content with highest exhibited by F15 formulation and depends on the 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 Dissolution Study

Fig. 1 shows that without coating (P1-P15), none of the batches give controlled release and release of drug limited

to 16 hours only, which are not meeting the objectives. All the batches show good and satisfactory release data and are selected for the next step for coating them. In porous osmotic pump tablets, the drug release rate depends on the concentration of the osmotic agent and pore former used. The osmotic agent concentration increases, then osmotic pressure created inside the tablet *also* increases; 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 pore former is added here in the 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 the coating layer. So here, the dual concepts of EOP and microporous were used for the release of the drug from tablets. The formulations (F1-F15) show that all 15 batches continue the drug release up to 24 hours and in that F15 is optimized with the release of 99.76% release profile as shown in Figs 1 and 2.

Release Kinetics

From the results (Figs 3-6), it is apparent that the regression coefficient value (R^2) of optimized formulation (F15) is closer to unity in the case of zero-order plot, i.e., 0.998 indicates that the drug release follows a zero-order mechanism. Hence it can be concluded that the major mechanism of drug release follows zero-order kinetics. The results conclude that the data follows the korsmeyerpeppas plot with an R^2 value equal to 0.9893

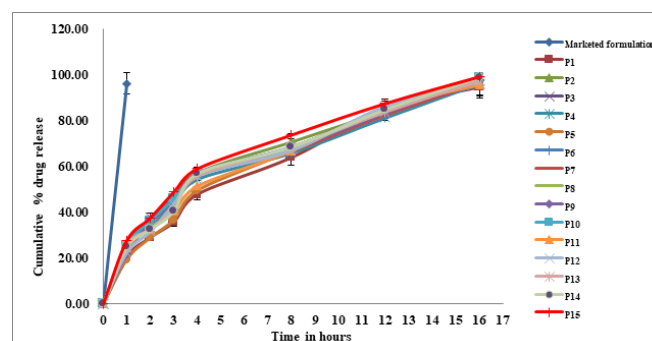


Fig. 1: Cumulative percentage drug release of repaglinide marketed formulation and repaglinide EOP core tablets (P1-P15)

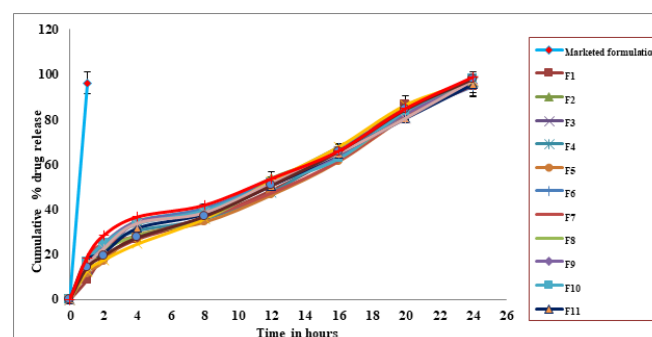


Fig. 2: Cumulative percentage drug release of repaglinide marketed formulation and repaglinide EOP coated tablets (F1-F15)

Drug Release Kinetics for Optimized Formulation F15

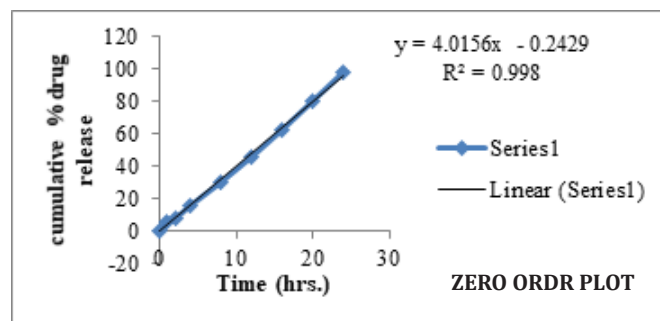


Fig. 3: % Drug release vs. time plot of F15 showing zero-order kinetics.

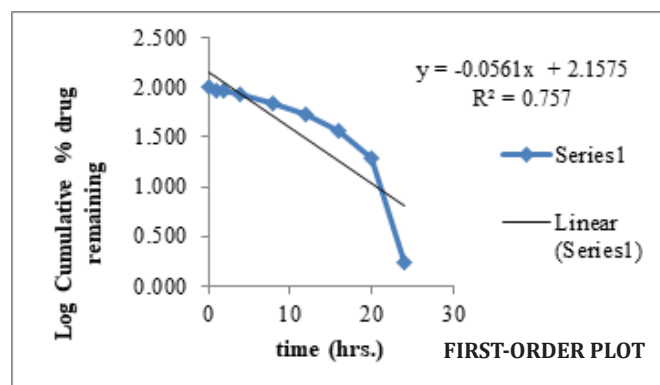


Fig. 4: Log % drug remained vs. time plot of F15 showing first-order kinetics

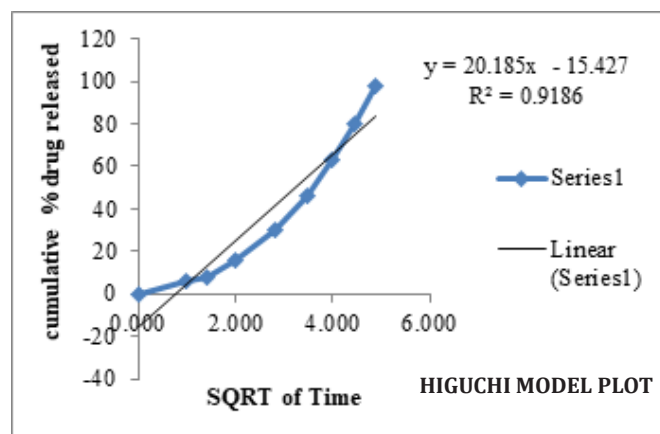


Fig. 5: %Drug release vs. square root of time plot of F15 showing Higuchi's model

and the n value obtained from the Korsmeyer-Peppas's plots, i.e., 1.4097 suggest that the drug release from tablets was anomalous non-Fickian diffusion super case II transport.

Marketed Formulation

From the above results (Figs 7-10) (R^2) value closer to unity in the case of first-order plot, i.e., 0.9799 indicates that the drug release follows the first-order mechanism. Hence it can be concluded that the major mechanism of drug release follows first-order kinetics.

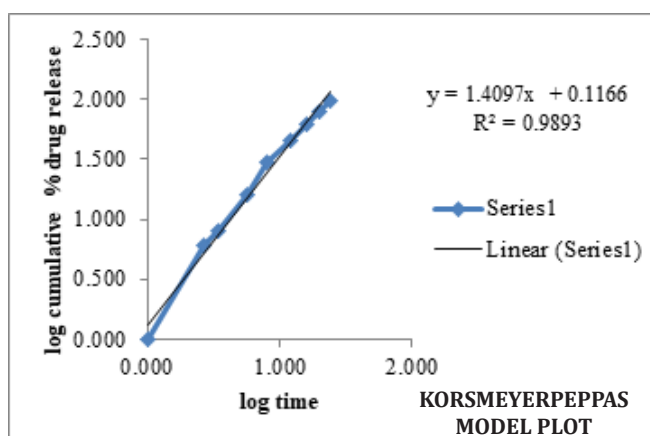


Fig. 6: Log %drug release vs. time plot of F15 showing Korsmeyer-Peppas's model

Marketed Formulation Release Kinetics

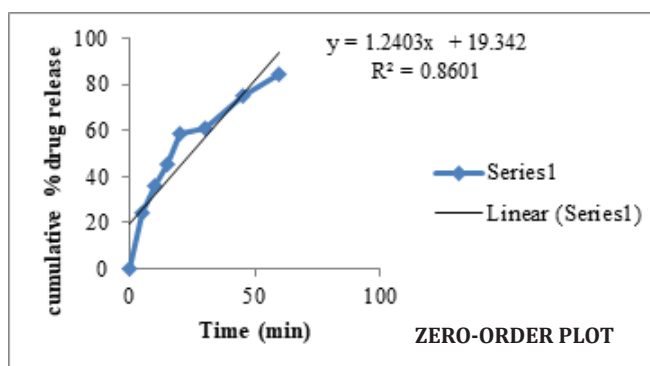


Fig. 7: %Drug release vs. time plot of marketed formulation showing zero-order kinetics.

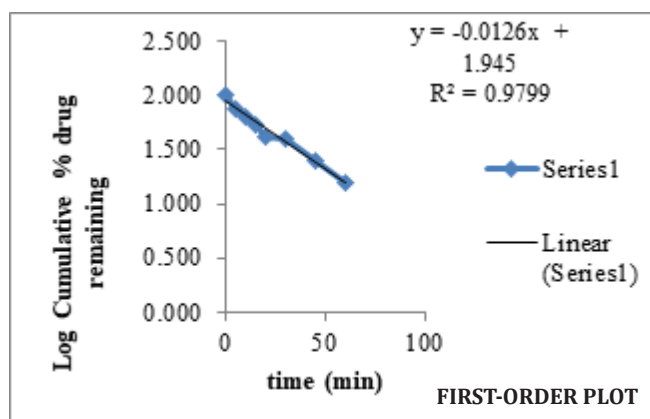


Fig. 8: %Drug release vs. time plot of marketed formulation showing first-order kinetics

FTIR Studies

The FTIR spectra of pure repaglinide showed the main characteristic peaks of amine: NH at $3500-3300\text{ cm}^{-1}$, -NH at $1660-1520\text{ cm}^{-1}$ and -C-H at $1350-1010\text{ cm}^{-1}$. The -C-N peaks of fatty amine can be located around $1260-1030\text{ cm}^{-1}$, while the -OH and -C-O peaks of the alcoholic hydroxyl group can be found at $3400-3100\text{ cm}^{-1}$ and wide stretch at $1270-1000\text{ cm}^{-1}$. The FTIR spectrum of repaglinide with



Table 5: Stability studies of f15 stored at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ 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 $\pm$ Standard Deviation; (n=3)

Table 6: Stability studies OFFFF 14 stored at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ 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 $\pm$ Standard Deviation; (n = 3)

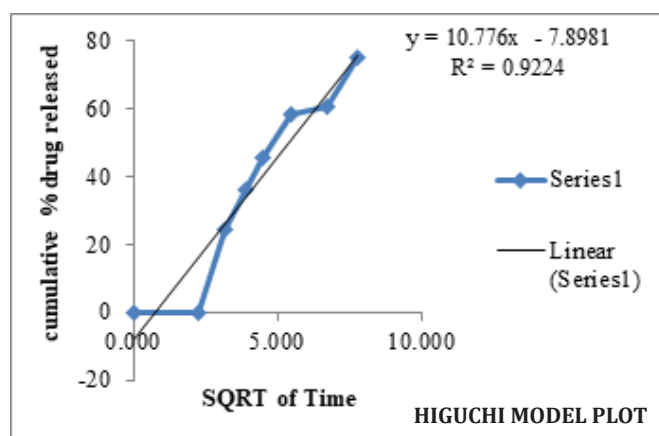


Fig. 9: %Drug release vs. square root of time plot of marketed formulation showing Higuchi's model

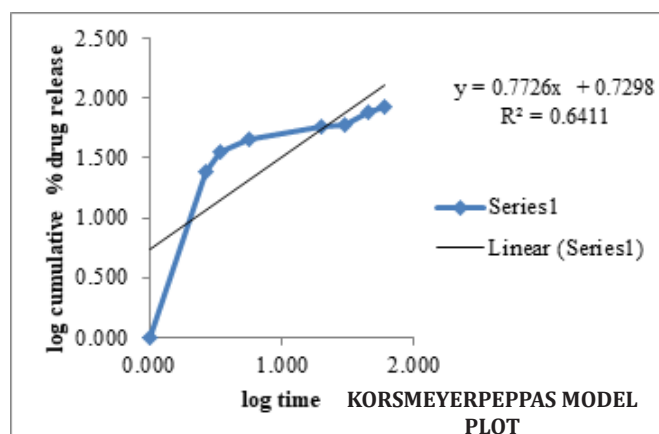


Fig. 10: Log %drug release vs. time plot of marketed formulation showing Korsmeyer-Peppas's model

HPMC K4M showed similar peaks at $3500\text{--}3400\text{ cm}^{-1}$, 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 $1100\text{--}1000\text{ cm}^{-1}$ was for stretching vibration of ethereal

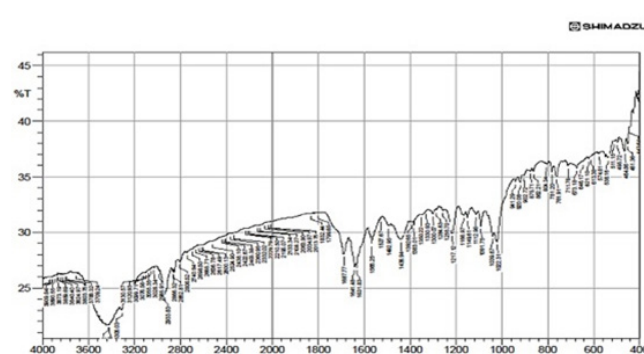


Fig. 11: FTIR Spectra of pure drug

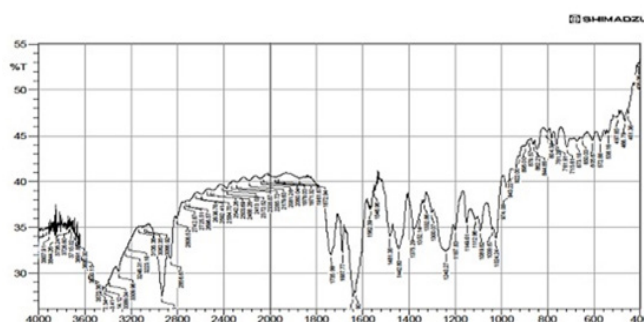


Fig. 12: FTIR Spectra of repaglinide optimized formulation (F15)

C-O-C groups. This confirms that all major peaks present in pure drug repaglinide are also present in optimized formulation F14 suggesting no significant interaction between them. (Figs 11 and 12).

Stability Studies

Optimized formulation (F15) was subjected to a stability study for 90 days at accelerated as per ICH guidelines. The optimized formulation was stable during 3 months period. Results indicate that the optimized formulation (F15) is stable with no variations in its physical properties (Tables 5 and 6).

CONCLUSION

Repaglinide osmotic tablets were prepared successfully by EOP and PPOP methods. In the EOP method, the drug release was mainly dependent upon osmogen in core, and pore-forming agent in coating, formulation F14 with high osmogen and pore-forming agent concentration exhibited the highest drug release of 99.76% for 24 hours was optimized. In the PPOP method, the drug release from the formulation was mainly dependent on the concentration of polymer, sub coating and enteric coating, and the release was independent of pH and agitational intensity; hence the formulation FF14 with the highest concentration of coating showed the highest drug release of 99.73% for 24 hours was optimized. Hence, it was revealed that the F15 and FF14 were optimized formulations that were used for further studies and evaluation. All formulations followed zero-order with Korsmeyer-Peppas kinetics, suggesting that the drug release from tablets was anomalous non-Fickian diffusion super case II transport. FTIR and SEM studies indicated insignificant interaction and porous nature of the formulation. Finally, optimized formulations were found to be stable after 3 months of storage under accelerated stability. Hence it is concluded that the repaglinide osmotic drug delivery system tablets can be formulated with a good release profile for a prolonged period of time up to 24 hours.

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