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(RESEARCH ARTICLE)

Formulation and evaluation of fast dissolving films of repaglinide solid dispersion

Naveen Balaji TSB, Bhagawati ST *, Manjunath K, Siddesh HM and Lakshith Raj PM

Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, B H Road, Tumakuru, Karnataka-572102, India.

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Abstract

The aim of the research work is to formulate fast dissolving films of repaglinide solid dispersion. The major problem of repaglinide is its low solubility. To enhance the solubility of the drug repaglinide, it is made into Solid dispersion by Solvent evaporation method by using polyethylene glycol 4000 as carrier. Prepared repaglinide solid dispersion is formulated into fast dissolving films by solvent casting method by using various hydrophilic polymers like hydroxy propyl methyl cellulose E-15, polyvinyl pyrrolidone K-30 and polyvinyl alcohol in different concentration and glycerol as plasticizer. The compatibility of the drug with the excipients was confirmed by Fourier transform infrared spectroscopy studies. Various evaluation parameters were done for all the formulated films. They are Physical appearance, Surface texture, Thickness uniformity, Folding endurance, Drug-Excipient interaction studies, Disintegration study, Drug content uniformity, *In-vitro* release study, Permeation study, Stability study. The optimized formulation F3 has shown satisfactory disintegration time of 40 seconds and *in-vitro* drug release of 98.72 % within 8 minutes.

Keywords: Repaglinide; Solid dispersion; Solvent evaporation method; Fast dissolving films; Solvent casting method

1. Introduction

Repaglinide is an anti-hyperglycaemic agent used for the treatment of Non-insulin dependent diabetes mellitus. It belongs to the short acting insulin secretagogues, which stimulates the release of insulin by binding with the β-cells of pancreas and controls the high blood sugar levels [1]. Repaglinide belongs to class II drugs in Biopharmaceutics Classification System (BCS), which has poor solubility in water, this results into poor bioavailability after oral administration and late onset of action [2].

Solid dispersions are mixture of a drug and an inert carrier, which are prepared to enhance the rate of dissolution and absorption of a poorly water soluble drug. Selection of water soluble carrier like polyethylene glycol 4000, will result in the fast release of the drug from the solid dispersion and increase the solubility of the drug in water. Solid dispersions prepared by solvent evaporation method involves dissolving the drug and carrier in the organic solvent, then organic solvent is removed by evaporating in low temperature. So this method has an advantage of preventing the thermal decomposition of both drug and carrier [3].

In late 1970's, Fast dissolving drug delivery system was developed alternative to conventional solid dosage forms for the purpose of better patient compliance to persons who suffers from dysphagia (Swallowing difficulty), paediatric and geriatric patients because they may also experience difficulties in swallowing the conventional oral solid dosage forms [4]. In recent times, Fast dissolving drug delivery system has emerged as a popular system because of its increased patient compliance, enhanced safety and efficacy [5].

On the basis of transdermal patches, oral fast dissolving films became a new drug delivery system for the oral delivery of drugs. After administration of the oral strip, the drug absorption takes place by Oro-mucosal route [6]. The oral mucosa is highly vascularized region, where the drug is rapidly absorbed into reticulated vein and the drug is put into

* Corresponding author: Bhagawati ST

the systemic circulation avoiding first pass metabolism, which leads in quick onset of action with enhanced bioavailability [7],[8]. So, In order to enhance the solubility, dissolution and absorption of the repaglinide, initially it was made into solid dispersion and then formulated into fast dissolving film.

2. Material and methods

Repaglinide pure drug, Hydroxy propyl methyl cellulose (HPMC E-15), Polyvinyl pyrrolidone K-30 (PVP K-30), Polyvinyl alcohol (PVA), Polyethylene glycol 4000 (PEG 4000) from yarrow chemicals, Mumbai. All other chemicals used were of analytical grade.

2.1. Fourier transform infrared spectroscopy (FTIR) studies

FTIR spectroscopy is used to check drug- excipient interaction study. The physical mixture of pure drug repaglinide and excipients were scanned in the instrument from the range of 4000-500 cm^{-1}. FTIR studies was performed using shimadzu FTIR 8300 spectrophotometer.

2.2. Preparation of repaglinide solid dispersion

Repaglinide solid dispersion is done by solvent evaporation method. Repaglinide and PEG 4000 is taken in a petridish along with methanol and gently heated and the mixture is stirred, then the solvent is evaporated and the mass is obtained which is sieved to obtain the repaglinide solid dispersion. PEG 4000 as carrier in different proportions 1:1, 1:2, 1:3 and 1:4 (drug: carrier) is used as shown in (Table 1).

Table 1 Formulation plan of repaglinide solid dispersions

SL.NO	Formulation	Drug : polymer (mg)
1	SD1	1:1
2	SD2	1:2
3	SD3	1:3
4	SD4	1:4

2.3. Characterization of repaglinide solid dispersion

2.3.1. Percentage practical yield

Percentage practical yield is calculated to know about the total percent yield, thus its helps in selection of appropriate method of formulation of solid dispersion. Solid dispersions were collected and weighed to determine the practical yield from the following equation.

$$\text{Percentage of practical yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \text{ X } 100$$

2.3.2. Drug content

10 mg of solid dispersion were accurately weighed and dissolved in 10 mL of methanol. The solution was filtered, diluted suitably and drug content was analysed at 283 nm by UV spectrophotometer. Each sample were analysed in triplicate. Actual drug content was calculated for all batches using the equation as follows.

$$\text{Percentage of drug content} = \frac{\text{Observed value}}{\text{Actual value}} \text{ X } 100$$

2.3.3. In-vitro drug release studies of solid dispersion

The release profile of drug present in the solid dispersion predicts how a delivery system might function and gives valuable insight into its *in-vivo* behaviour. *In-vitro* drug release profile for each type of solid dispersion (SD1-SD4) as well as pure drug was performed using United States Pharmacopoeia (USP) type 2 dissolution apparatus. Sample equivalent to 2 mg of repaglinide was added to 300 mL of simulated saliva of pH 6.8 at 37±0.5 °C and stirred at 75 rpm. Aliquot of 2 mL was withdrawn at time intervals of 15, 30, 45 and 60 min. The withdrawn volume was replenished with the same volume of dissolution medium simulated saliva of pH 6.8 in order to keep the total volume constant. The

absorbance of the samples was measured at λ max 283 nm after suitable dilution if necessary, using appropriate blank. Results of *in-vitro* drug release studies obtained from absorbance data were shown graphically as cumulative percentage drug released versus time.

2.4. Formulation of fast dissolving films

Repaglinide (RPG) therapeutic dose was 2 mg, the optimized RPG:PEG 4000 solid dispersion (SD4- 1:4 ratio) with equivalent weight 24 mg of repaglinide was dissolved in the polymeric solution, after complete dissolution of the solid dispersion, glycerol (plasticizer) was added and stirred to form a homogeneous solution. Finally vanillin and sodium saccharin are added and stirred to form a homogeneous mixture. The solution was casted in a mould 6×8 cm (length and width). Then kept in hot air oven at 60 ºC for 24 hours. The film thus formed was cut into size of 2×2 cm square strips. The prepared square thin film strips were stored in desiccators for further studies .The detailed compositions of the repaglinide oral films are given in table 2.

Table 2 Formulation details of repaglinide fast dissolving oral film

Formulations	RPG:PEG 4000 (S.D)	Polymer and its composition (mg)			Glycerol (mL)	Sodium saccharin (mg)	Vanillin (mg)	D.water (mL)
		HPMC E-15	PVP K-30	PVA				
F1	120	120			0.1	2	2	10
F2	120	240			0.1	2	2	10
F3	120	360			0.1	2	2	10
F4	120	80	40		0.1	2	2	10
F5	120	120	120		0.1	2	2	10
F6	120	270	90		0.1	2	2	10
F7	120	80		40	0.1	2	2	10
F8	120	120		120	0.1	2	2	10
F9	120	270		90	0.1	2	2	10

2.5. Evaluation of fast dissolving films

2.5.1. Physical appearance and surface texture of films

This parameter was checked simply by visual inspection of films and evaluation of texture by feel and touch.

2.5.2. Weight uniformity of films

Three films of the size 2×2 cm were cut and weighed individually using digital balance and the average weights of films were calculated.

2.5.3. Thickness of films

Thickness of the films was measured by using screw gauge with a least count of 0.01 mm at different spots of the films. The thickness was measured at three different spots in the films and the average was noted.

2.5.4. Folding endurance of films

The flexibility of films can be measured quantitatively in terms of folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 2x2 cm) at the same place till it brakes. The number of times films could be folded at the same place, without breaking of film provides the value of folding endurance.

2.5.5. Drug-polymer interaction study of films

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. FTIR spectroscopy is one of the most used analytical techniques which identifies the possibility of chemical identification. Infra-red spectra of pure drug repaglinide and formulations were scanned by using FTIR method.

2.5.6. Disintegration study

In-vitro disintegration test of films is performed to check how fast the films are disintegrated in the simulated saliva of pH 6.8.

2.5.7. Drug content uniformity of films

The films were tested for drug content uniformity by UV Spectrophotometric method. Films of 2×2 cm size were cut from three different places from the casted films. Each film was placed in 100 mL volumetric flask and dissolved in simulated saliva pH 6.8 and 2 mL is taken and diluted with water up to 10 mL. The absorbance of the solution was measured at λ max 283 nm using UV/ visible spectrophotometer (Shimadzu). The percentage drug content of the film was determined.

2.5.8. In-vitro drug release study

The release rate of repaglinide fast dissolving oral films was determined by using USP dissolution testing apparatus II at 50 RPM. The film with 2×2 cm was placed in the 300 mL of 6.8 pH simulated saliva as dissolution medium, and temperature was maintained at 37 °C. From this dissolution medium, 2 mL of the sample solution was withdrawn at different time intervals. The samples were filtered through Whitman filter paper and absorbance was determined 283 nm using double beam UV- Visible spectrophotometer.

2.5.9. Permeation study

The prepared fast dissolving oral films are placed in the diffusion cell on the upper membrane of the (donor compartment) and the receptor compartment contain a simulated saliva (10 mL) it can be contact with the dialysis membrane. Upper side of the donor compartment contain a film of length and width (2×2) cm it contain 2 mg of drug and the receptor compartment contains simulated saliva and magnetic bead and this diffusion compartment placed in the magnetic stirrer the drug permeation start through the dialysis membrane and enter in to the receptor compartment. From the receptor compartment, 2 mL is taken every 5 minutes up to 45 minutes and maintain the sink condition by replace the 2 mL of simulated saliva in to the receptor compartment and samples were analysed by (Shimadzu) Uv-visible spectrophotometer.

2.5.10. Stability studies

The purpose of stability testing is to prove evidence on how the quality of the drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per International Council for Harmonisation (ICH) guidelines. The formulated fast dissolving oral films were wrapped in aluminium foil and stored at 45±0.5 ºC for period of twelve weeks. After the period of twelve weeks films were tested for appearance, drug content and *in-vitro* drug release.

3. Results and discussion

3.1. Preparation of standard graph of repaglinide using simulated saliva of pH 6.8

Repaglinide showed maximum absorbance at 283 nm in simulated saliva of pH 6.8 using UV- Spectrophotometer. Based on this information, a standard graph was plotted (Figure 1). The obtained correlation coefficient was 0.9991 and the regression equation y = 0.0095x.

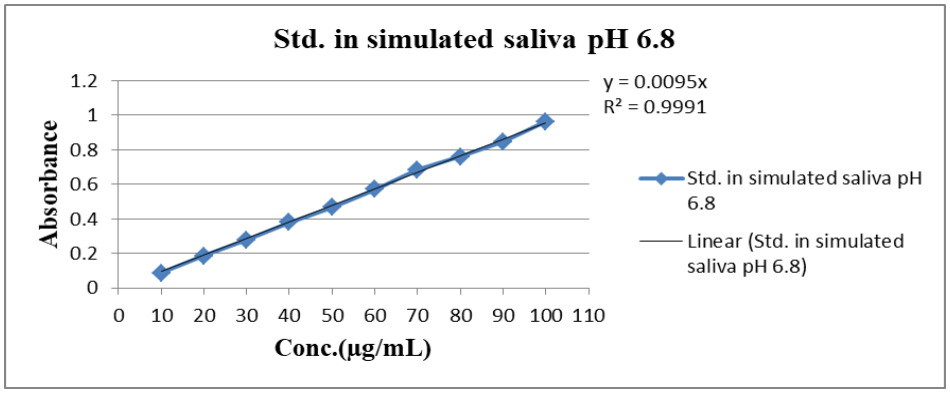

Figure 1 Standard calibration curve of repaglinide in simulated saliva of pH 6.8

3.2. FTIR studies

FTIR spectra of pure drug repaglinide, and combination with HPMC E-15, PVP K-30, PVA, PEG 4000 were shown in the (Figure 2-6). Pure drug repaglinide showed principal absorption peaks at 3308.03 cm^{-1}(amine stretching), 2935.76 cm^{-1}(C-H aromatic stretching), 2850.88 cm^{-1}(C-H aliphatic stretching), 2804.59 cm^{-1}(carboxylic OH stretching) 1689.70 cm^{-1}(C=O stretching), 1635.69 cm^{-1}(C=O stretch of amide & esters), 1489.10 cm^{-1}(C=C stretching), 1215.19 cm^{-1}(C-N stretching), 1147.68 cm^{-1}(ether linkage (R-O-R'), 1089.82 cm^{-1}(C-N amine stretching). All the peaks obtained in the pure drug repaglinide were retained in the mixture of drug and excipients, this revealed that the drug is compatible with the used excipients.

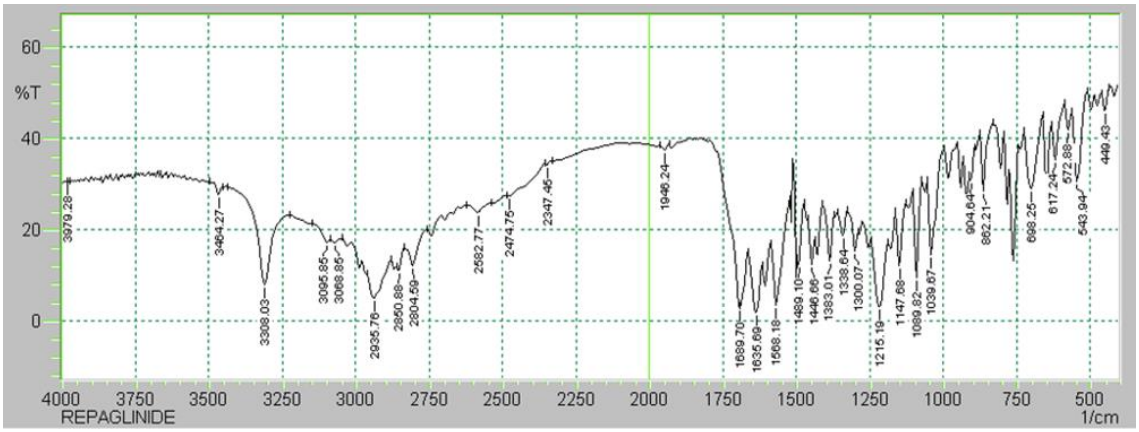

Figure 2 FTIR spectrum of pure drug repaglinide

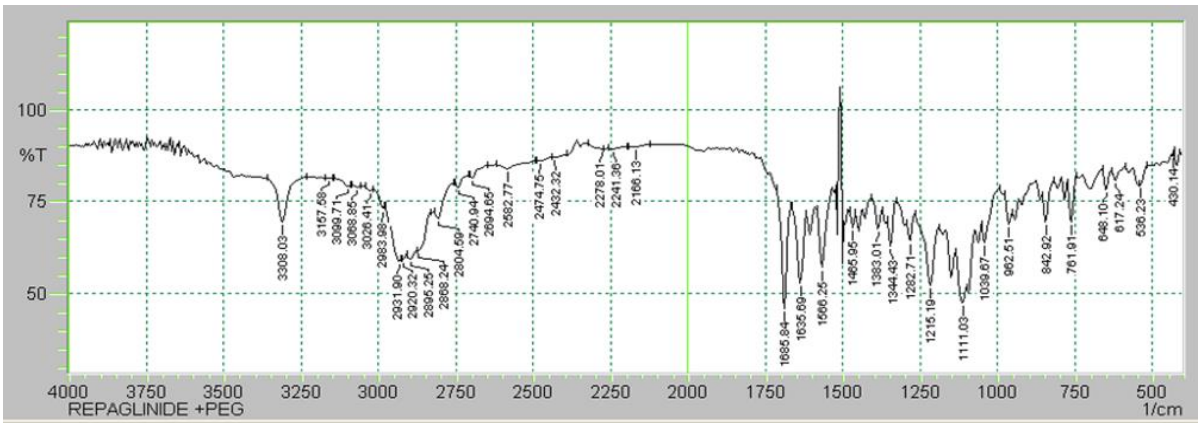

Figure 3 FTIR spectrum of repaglinide + PEG 4000

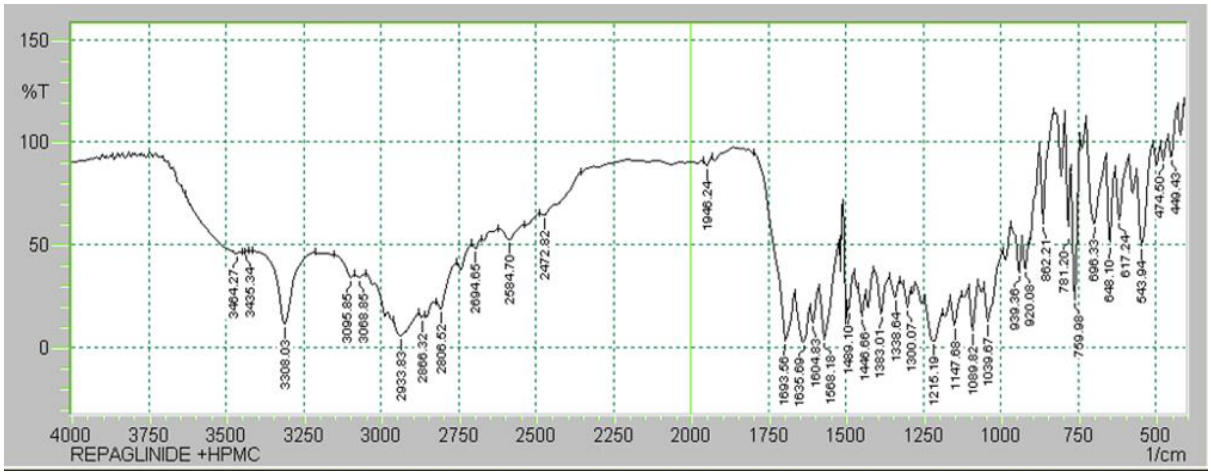

Figure 4 FTIR spectrum of repaglinide + HPMC E-15

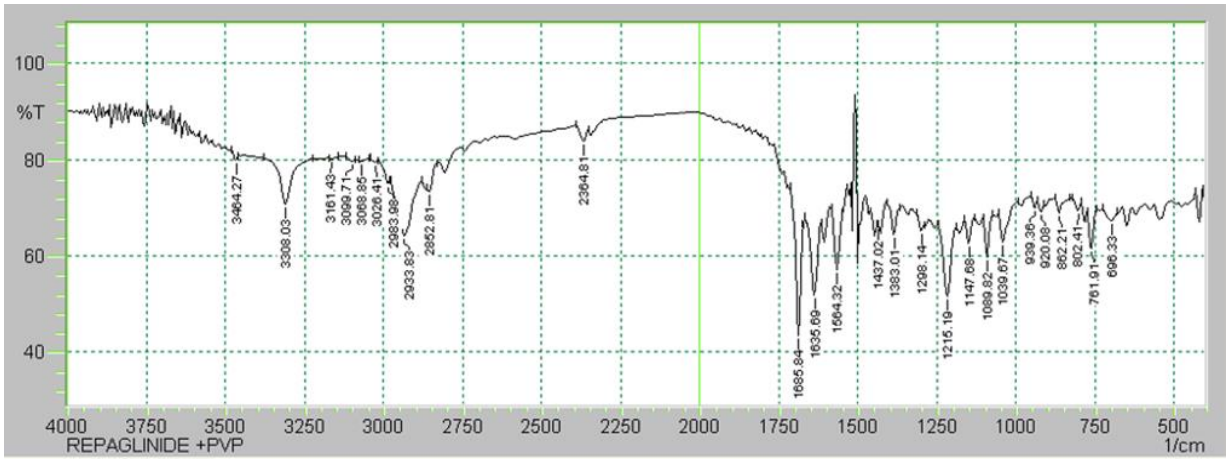

Figure 5 FTIR spectrum of repaglinide + PVP K-30

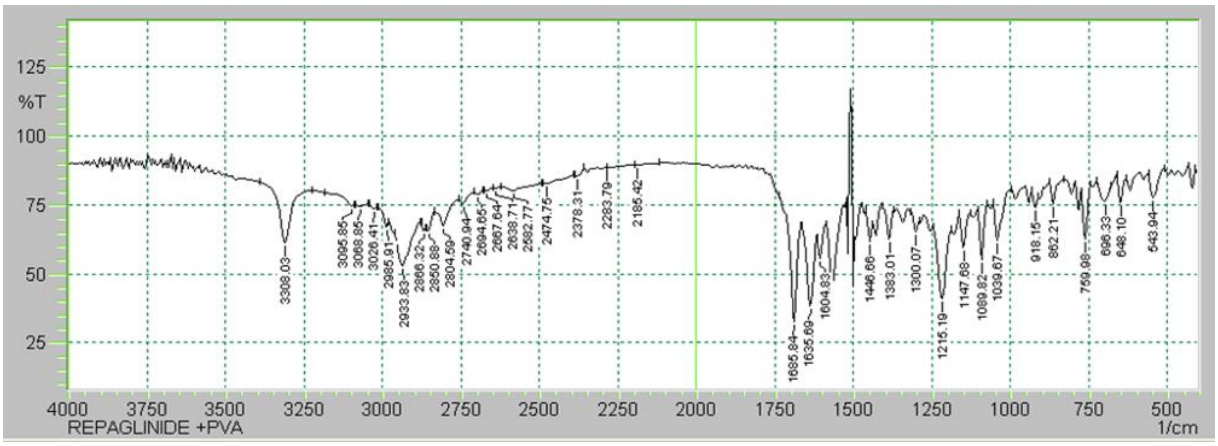

Figure 6 FTIR spectrum of repaglinide + PVA

3.3. Selection of optimized solid dispersion for films

Among all the four formulations of solid dispersions i.e. SD1, SD2, SD3 and SD4, the optimized formulation was SD4 which showed maximum % practical yield, drug content and percentage drug release compared to other formulations (Figure 7, 8, 9 and Table 3). These optimized repaglinide: poly ethylene glycol 4000 solid dispersions (RPG: PEG 4000) at weight ratio of 1:4 prepared by solvent evaporation method was selected for this study. It was proposed to formulate

and develop the fast dissolving films. The formulated FDFs (Fast dissolving film) were clear, homogeneous, some were transparent and some were partially transparent. They were found be physically flexible and dry.

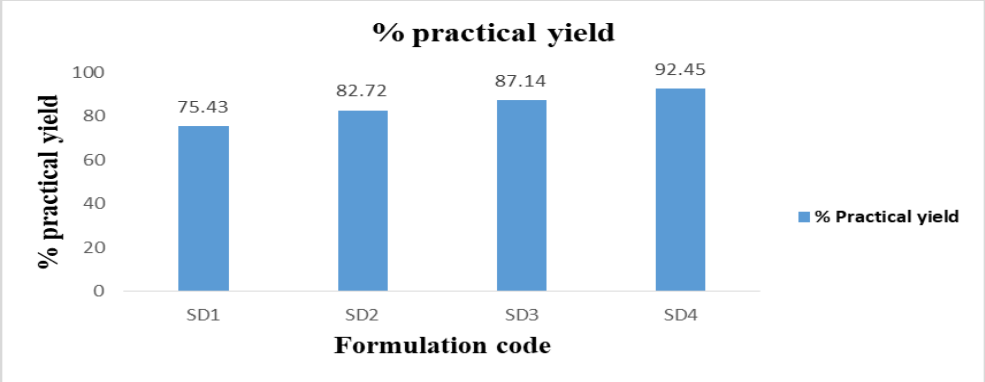

Figure 7 % practical yield of solid dispersions

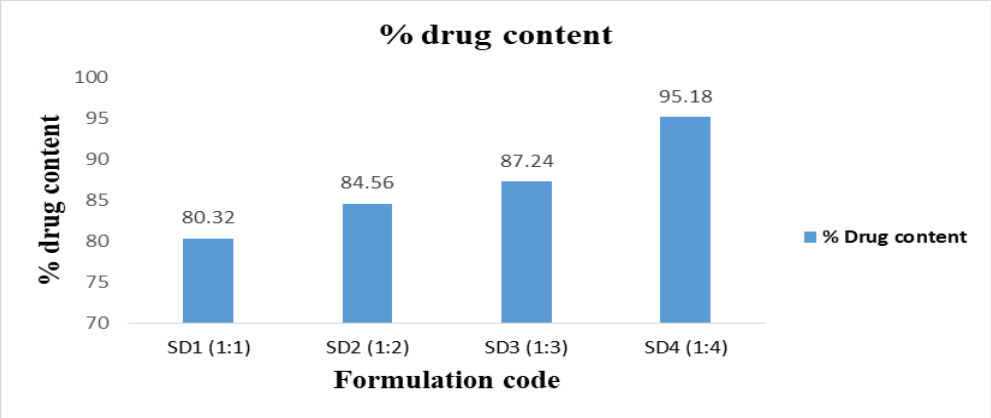

Figure 8 % drug content of solid dispersions

Table 3 *In-vitro* drug release data of solid dispersions

SL.NO	Time (min)	% cumulative drug release (% CDR)				
		Pure drug	SD1(1:1)	SD2(1:2)	SD3(1:3)	SD4(1:4)
1	15	18.84	25.92	39.71	48.92	56.37
2	30	43.10	37.63	50.45	58.20	70.62
3	45	50.21	45.84	58.20	69.54	83.19
4	60	50.27	55.14	70.90	79.20	94.05

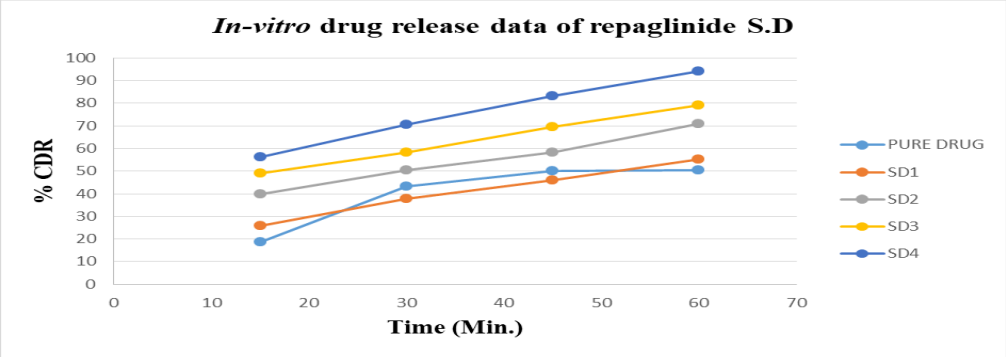

Figure 9 *In-vitro* drug release profile of solid dispersions of repaglinide

3.4. Weight uniformity

The randomly selected film strips of 2 × 2 cm areas were cut at different places from the casted film and weight was measured. Weight of film strip units varies from 46.95 to 51.07 mg. The results indicated that all the formulated films were almost in same weights and difference in their weights were because of the concentration of the polymer which were used in the film (Table 4).

3.5. Folding endurance

Folding endurance was found to be highest for F6 and lowest for F7. The folding endurance values of the FDF were found to be optimum and therefore, the FDFs exhibited the good physical and mechanical properties. The folding endurance of films was found to be in the range of 229 to 272 folds (Table 4).As all the formulations contain different amount of polymers, the thickness was gradually increased with the increase in the amount of polymers.

3.6. Thickness uniformity

All the film formulations were found to have thickness in the range of 0.15 to 0.24 mm, thickness increased with increase in polymer concentration and they were observed within the limits.

3.7. Drug content

The prepared film formulations were evaluated for their drug content in UV/ visible spectrophotometer. The drug was dispersed in the range of 92 % to 98 %. This showed that drug was uniformly dispersed in all films. (Table 4).

3.8. Disintegration study

It was observed that disintegration time varies from 35 to 46 sec for all the formulations (Table No.4). *In-vitro* disintegration time of FDFs was affected by polymers viz. HPMC E-15, PVP K-30 and PVA. This is due to polymer's high water absorption and retention capacities.

Table 4 Evaluation data for fast dissolving films

Sl.No	Formulation code	Weight variation (mg)	Thickness (mm)	Folding endurance	%drug content	Disintegration time
1	F1	47.29±0.045	0.153±0.011	263.00±1.00	95.60±0.14	35.00±1.00
2	F2	49.1±0.815	0.20±0.017	264.66±0.57	96.45±0.21	37.66±0.57
3	F3	50.55±0.099	0.243±0.005	271.33±0.57	98.79±0.14	40.66±0.57
4	F4	46.95.±0.592	0.163±0.011	232.00±1.73	94.34±0.27	37±1.00
5	F5	50.02±0.243	0.196±0.015	239.66±1.15	95.52±0.24	41.33±1.15
6	F6	50.91±0.165	0.233±0.005	272.33±1.52	95.23±0.17	45.66±1.52
7	F7	48.49±0.312	0.176±0.005	229.66±1.52	92.31±0.20	37.33±0.57
8	F8	50.81±0.590	0.196±0.011	238.33±0.57	93.50±0.22	43.66±1.15
9	F9	51.07±0.387	0.226±0.005	242.33±1.52	94.73±0.14	46.66±1.52

Results are expressed in terms of mean ± standard deviation (n =3).

3.9. *In-vitro* drug release studies

The formulation F3 film containing HPMC E-15 as hydrophilic polymers showed highest percentage of drug release (98.72%) within 8 minutes compared to that of films containing HPMC E-15 combined with PVP K-30 and PVA as a polymers.(Table 5 and 6).

Table 5 *In-vitro* release data of various repaglinide fast dissolving oral films

Time (min)	% cumulative drug release				
	F1	F2	F3	F4	F5
2	39.36±0.14	31.28±0.22	45.30±0.14	37.33±0.24	35.61±0.15
4	46.19±0.21	52.12±0.25	75.80±0.19	43.41±0.10	48.24±0.11
6	66.66±0.12	70.72±0.17	91.90±0.20	51.56±0.16	55.89±0.28
8	81.46±0.20	86.48±0.10	98.72±0.18	63.82±0.21	67.27±0.27
10	93.25±0.18	96.21±0.23	-	75.50±0.25	77.91±0.13
12	-	-	-	82.67±0.12	85.19±0.17
14	-	-	-	87.85±0.22	89.14±0.21
16	-	-	-	-	-
18	-	-	-	-	-
20	-	-	-	-	-

Results are expressed in terms of mean ± standard deviation (n =3).

Table 6 *In-vitro* release data of various repaglinide fast dissolving oral films

Time (min)	% cumulative drug release			
	F6	F7	F8	F9
2	42.43±0.20	21.34±0.16	25.32±0.14	23.64±0.14
4	50.54±0.15	30.95±0.11	34.46±0.13	31.12±0.12
6	61.29±0.19	40.63±0.16	43.32±0.16	48.25±0.25
8	72.14±0.22	51.11±0.20	48.03±0.21	55.59±0.28
10	80.67±0.12	59.37±0.22	55.81±0.24	61.41±0.10
12	84.25±0.18	60.55±0.15	65.69±0.19	66.71±0.27
14	89.51±0.10	65.05±0.14	70.10±0.28	72.24±0.14
16	-	72.71±0.24	76.51±0.21	80.28±0.16
18	-	80.21±0.20	84.19±0.14	86.64±0.12
20	-	83.18±0.15	86.15±0.18	88.34±0.17

Results are expressed in terms of mean ± standard deviation (n =3).

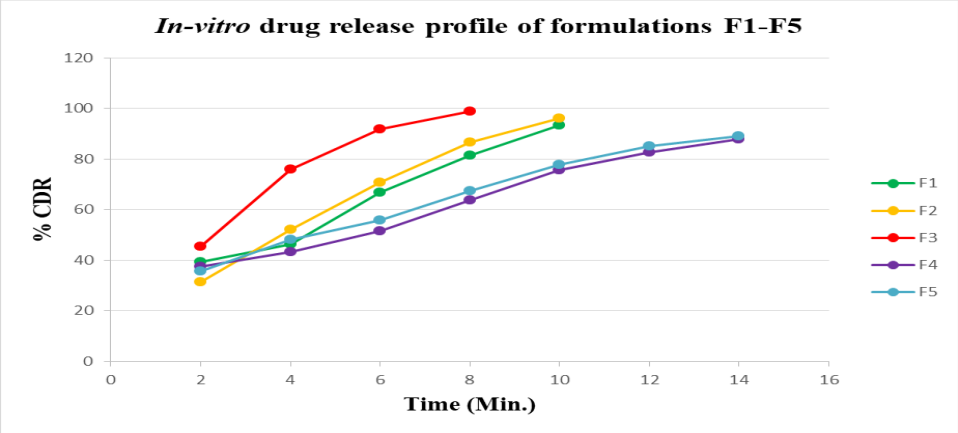

Figure 10 *In-vitro* drug release profile of formulations F1-F5

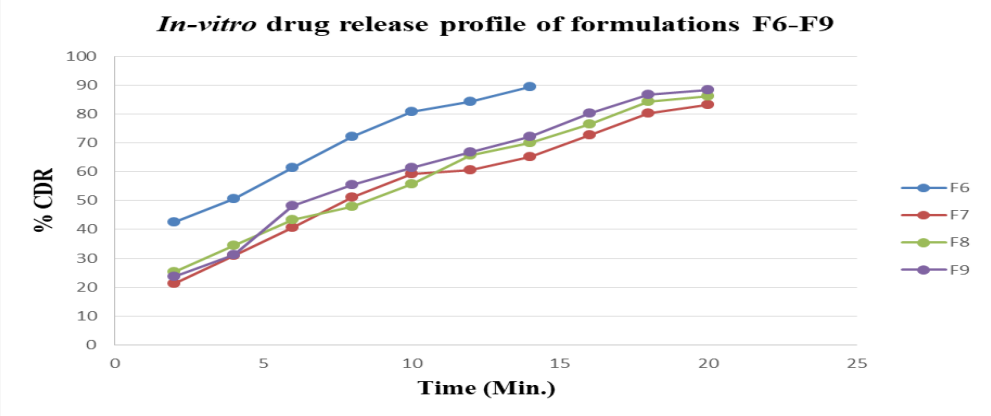

Figure 11 *In-vitro* drug release profile of formulations F6-F9

3.10. Drug permeation study

The formulation F3 containing HPMC E-15 has showed permeation of 93.56 % in 35 minutes, which is highest percentage with least time than the other formulations. (Table 7 and 8).

Table 7 Drug permeation study data of F1-F5

Time (min)	% cumulative drug release				
	F1	**F2**	**F3**	**F4**	**F5**
5	42.15	38.81	40.54	40.21	36.61
10	51.46	48.70	53.61	48.51	42.52
15	59.28	56.84	60.47	55.86	50.95
20	69.39	64.36	70.12	60.31	61.10
25	76.85	72.34	81.19	68.49	70.65
30	81.75	80.63	86.84	75.55	78.81
35	85.36	84.36	93.56	81.56	82.90
40	88.51	89.64	-	85.45	86.15
45	-	-	-	-	-

Table 8 Drug permeation study data of F6-F9

Time (min)	% cumulative drug release			
	F6	F7	F8	F9
5	36.34	39.45	35.63	38.57
10	48.24	46.51	42.67	45.62
15	60.62	56.35	51.54	53.18
20	72.51	63.75	60.10	66.86
25	80.72	71.14	68.96	73.77
30	84.56	76.72	73.35	79.36
35	86.62	79.62	78.49	81.14
40	89.46	83.48	81.28	86.12
45	-	-	-	-

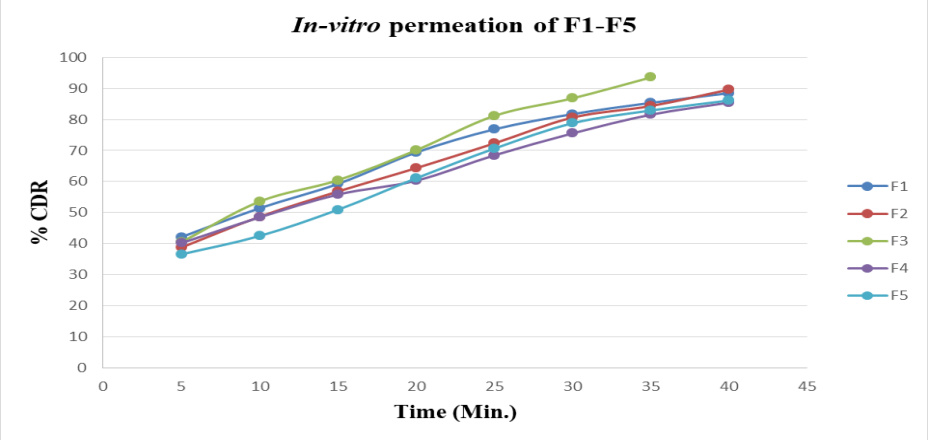

Figure 12 *In-vitro* permeation profiles of F1-F5.

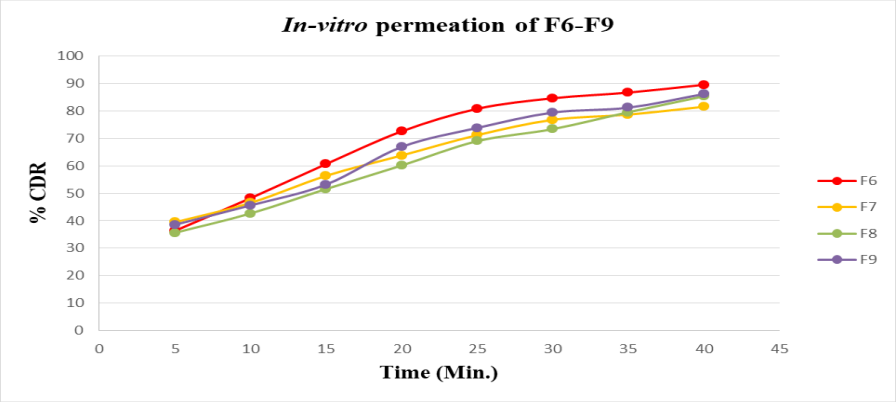

Figure 13 *In-vitro* permeation profiles of F6-F9

3.11. Stability study

In-vitro release study was performed for the optimized formulation F3 after 4, 6 & 12 weeks showed good stability. (Table 9).

Table 9 *In-vitro* release data of stability study of formulation F3

Time (min)	% cumulative drug release			
	1St Day	After 4weeks	After 6 weeks	After 12 weeks
2	45.27	44.39	45.94	43.27
4	75.53	75.10	74.24	73.53
6	91.81	92.25	90.12	91.54
8	98.65	98.70	98.18	98.51

4. Conclusion

Fast dissolving films are becoming more popular, emerging dosage form and have greater importance to treat emergency cases like Diabetes, Hypertension and wherever the fast onset of action is required. FDF are much more beneficiary for paediatric and geriatric patients. In this Study, the drug Repaglinide is made into solid dispersion by using PEG 4000 as a carrier in different quantities, Optimized solid dispersion formulation SD4 (1:4) has been incorporated in fast dissolving film. Among all the formulations, Repaglinide oral fast dissolving film containing HPMC E-15 polymer F3 has showed higher percentage of drug release (98.72 %) within 8 minutes, it showed better permeation and better physical properties.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that, there is no conflict of interest exist in this research article.

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