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Formulation and Evaluation of Multiple Emulsion of Repaglinide

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ABSTRACT: Repaglinide (Prandin) is an oral insulin secretagogue of the meglitinide class (Antidiabetic) of BCS Class II has low bioavailability. It is used to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood). The Multiple Emulsion is the complex polydispersed system in which an emulsion is incorporated in another emulsion therefore they are also known as "*Emulsion of Emulsion*". The aim was to prepare a stable Multiple Emulsion of Repaglinide by incorporating various hydophilic and lipophilic surfactants at different concentrations. The characterization of drug sample was done using spectrophotometric analysis and melting point determination. All the observations and recorded data were identical to the values reported in literature. Calibration curves of Repaglinide in 0.1N HCl and phosphate buffer (pH 7.4) were prepared using a double beam UV-visible spectrophotometer (Shimadzu 1800)The different formulations of multiple emulsion were evaluated on the basis of their drug entrapment efficiency and stability. The multiple emulsion was stable and had good entrapment efficiency. There were no drug-excipients interactions. From the result and conclusion of the research work we can summarize that the multiple emulsions can be optimized for good stability and higher entrapment efficiency by optimizing different formulation variables like type and proportion of primary and secondary emulsifier incorporated in Primary Emulsion and Multiple Emulsion

Keywords: Repaglinide, Multiple Emulsion, UV-visible spectrophotometer, Antidiabetic

INTRODUCTION

The multiple emulsions are named as 'emulsions of emulsions' where the coexisting of both phases of single emulsions namely water-in-oil and oil-in-water takes place. Such complex poly-dispersed system was firstly described by William Seifriz (1925). Since then, the formulations, stability, characterization and extension of application areas have been studied in detail. Nevertheless, there is still need to study multiple emulsion concept and possible applications due to inadequate number of researches. The concept of multiple emulsions is based on dispersing a single emulsion into another phase. There are two main types of

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multiple emulsions which are water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O). There is a dispersed phase as well as continuous phase for each type of multiple emulsions. For the case W/O/W, oil droplets containing smaller water droplets are dispersed in continuous water phase. Likewise, small oil globules are entrapped in the first water phase and these oil-water globules are further dispersed in continuous oil phase to form O/W/O type of multiple emulsions[1].Multiple Emulsions have been employed for controlled and prolonged release of drugs from formulations[2,3,4]and as intermediate step in microencapsulation process.[5] Drugs that have unpleasant taste such as bitterness have also been incorporated in the
internal phase of a multiple emulsion system to mask the taste.[6] The basic rationale for these applications is that the drug has to transverse interfacial barriers and other phases (than where it was incorporated) before its liberation from the formulation and subsequent bioavailability.[7]
Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance.[8] Repaglinide is an oral bloodglucose-lowering drug of the meglitinide class use to treat NIDDM (noninsulin-dependent diabetes mellitus). It lowers blood glucose by stimulating the release of insulin from the pancreas. It has an extremely short half life of 1 h. In addition, the oral bioavailability of Repaglinide is low (56%) due to extensive hepatic first-pass effect. Dosage frequency of Repaglinide is 0.5 to 4 mg in 3 to 4 times in a day. The purpose of the present work was to develop multiple emulsion of Repaglinide which increases the patient compliance and also sustain the release of drug to increase the bioavailability.

MATERIALS AND METHOD

1. MATERIALS

Repaglinide was obtained from Yarrow chem. pvt. Ltd. Span 40 was obtained from Hymedia Laboratories Span 60, 80 and Tween 80 was obtained from Merch Laboratories and Heavy liquid Paraffin from Renkem .

2. PREFORMULATION STUDIES:

2.1 Identification of Drug

2.1.1 Organoleptic Characteristics:

The drug samples obtained were examined for their state, appearance, colour**,** odour, taste etc.

2.1.2 Melting point Determination:

The melting point of the drug substances was determined by using capillary tube method. In this small amount of Repaglinide powder was taken in a closed end capillary tube and placed

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in melting point apparatus. The temperature was gradually increased and under closed observation the temperature at which the powder completely melts was successfully detected. The temperature at which the powder melts is recorded as melting point of Repaglinide.

2.1.3 By UV Spectroscopy

UV- Spectrum of pure Repaglinide was taken in 0.1 N Hcl (pH 1.2) as a medium. Drug (10 mg) was dissolved in 100 ml 0.1 N Hcl to obtain the stock solution of concentration 100µg/mL From this stock solution, 1mL was withdrawn and diluted upto 10 mL and resultant solution was scanned between 200-400 nm using UV- spectrophotometer.[9]

2.1.4 Preparation of Calibration Curve

Preparation of standard curve for Repaglinide in phosphate buffer (pH 6.8) and in 0.1 N HCl solution.

Standard Plot for Repaglinide:[10]

Standard Graph by using 0.1N HCl :

Accurately weighed 10 mg of Repaglinide was dissolved in 100 ml of 0.1 N HCl buffer solution to form 100 µg/ml stock solution. From this stock solution aliquots of 2.5 ml, 5 ml, 7.5 ml, 10 ml, 12.5 ml, 15 ml,17.5 ml, 20 ml, 22.5 ml, 25 ml, were pipetted out into a series of 25 ml volumetric flask and volume was made up to 25 ml in order to get a concentration ranging from 5-25µg/ml. The absorbance of the resulting solution was then measured at 288nm using UV spectrophotometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance V/s. concentration in µg/ml.

Phosphate Buffer (pH 6.8):

Accurately weighed 10 mg of Repaglinide was dissolved in 100 ml of 6.8 pH buffer solution to form 100 µg/ml stock solution. From this stock solution aliquots of 2.5 ml, 5 ml, 7.5 ml, 10 ml, 12.5 ml, 15 ml,17.5 ml, 20 ml, 22.5 ml, 25 ml, were pipetted out into a series of 25 ml volumetric flask and volume was made up to 25 ml in order to get a concentration ranging from 5-25µg/ml.

The absorbance of the resulting solution was then measured at 288nm using UV spectrophotometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance V/s. concentration in µg/ml.

2.1.5 IR absorption spectrum:

FT-IR spectra of drug sample were recorded using potassium bromide (KBr) pellet method at resolution of 4cm^{-1} for its authentication and to study principle peaks using FT-IR spectrophotometer (FT-IR 8400S, Shimadzu). Dry sample of drug and potassium bromide was mixed uniformly and filled into the die cavity of sample holder and an IR spectrum was recorded. The identified peaks were compared with the principle peaks of reported IR spectrum. Thus the samples were authenticated.[12]

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2.1.6 Solubility studies of drug:

The sample was qualitatively tested for its solubility in various solvents. It was determined by taking 10mg of drug sample in 10ml of solvent as 0.1 N Hcl, phosphate buffer pH 6.8, alcohol, acetone, methanol, ethanol etc.[13]

2.1.7 Evaluation of Solid dispersion:

100mg of Repaglinide with 300mg β-CD in 1:3 ratio was taken. β -CD was taken to the mortar-pestle. Subsequently drug was incorporated slowly into it and trituration was further continued for one hour and passed through sieve no. # 60.

2.1.8 Drug and Excipient Interaction Studies:

The compatibility of the drug was assessed by drug-excipient interaction study. The drug was mixed with various excipients in a 1:1 ratio in glass vials which were properly sealed and kept undisturbed at 40ºC temperature for 14 days. After 14 days incompatibility was confirmed by TLC.[14]

2.2 Formulation development of multiple emulsion of Repaglinide:

2.2.1 Procedure:

- Multiple emulsions were prepared by two step emulsification process: a) Preparation of primary emulsification; b) Secondary emulsification [15-16]

a) **Primary emulsification**: 10 ml of distilled water containing 25 mg of drug was gradually added to 14 ml of oil phase containing primary emulsifier (Span40, Span60, and Span 80) and 25mg of drug with continuous stirring at 5000 rpm for 5 minutes. It gives the primary emulsion.

b) **Secondary emulsification**: 20 ml of viscous primary emulsion was emulsified further with an external aqueous phase containing secondary emulsifier (Tween80) and 50 mg drug with continuous stirring at 1000 rpm for 10 min. All the formulations were prepared by following the same procedure. Effect of primary emulsifier was observed by evaluating several formulations.

2.3 Evaluations and Formulations:

1. Globule size:

In this study, globule sizes of the multiple emulsions prepared were determined using light microscope fitted with a digital camera for the freshly prepared emulsions and for the emulsions kept at different conditions for 28 days [17]

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2. Entrapment efficiency

Percentage Entrapment Efficiency (% EE) was determined by taking freshly prepared W/O/W multiple emulsions and immediately centrifuged at 4000 rpm for 10 min. Then 1ml of the aqueous phase (the lower layer) was precisely withdrawn through 2 ml hypodermic syringe and diluted properly with phosphate buffer 6.8. The solution was filtered with a Millipore filter (0.22 mm in pore size) and drug content was analyzed on UV spectrophotometer at 287.6 nm.[18]

The Encapsulation Efficiency was determined by following equation:[19]

$$\% EE = \frac{[\text{Total drug incorporated} - \text{Free Drug}]}{\text{Total drug}} \times 100$$

3. Stability tests:

Stability tests were performed at different storage conditions for both primary and multiple emulsions. The tests were performed on samples kept at 8 ± 0.1 OC (in refrigerator), 25 ± 0.1 OC (in oven), 40 ± 0.1 OC (in oven) and 40 ± 0.1 OC at 75% relative humidity (RH) (in stability cabin).

4. Organoleptic characteristics:

Freshly prepared primary and multiple emulsions were investigated organoleptically (color, liquefaction and phase separation). Organoleptic characteristics of both primary and multiple emulsions kept at different storage conditions, i.e. color, liquefaction and phase separation were noted at various intervals, i.e. 0 h, 1 h, 1 day, 3 days, 7days, 14 days, 21 days and 28 days for 28 days.

5. Microscopic tests

Multiple emulsions were analyzed under the microscope to confirm the multiple characters. A drop of multiple emulsions was placed on the glass slide, diluted with water and covered by a glass cover. A drop of immersion oil was placed on the cover slide and observed under the microscope.[17]

6. pH determination

The pH value of the freshly prepared emulsions and the emulsions kept at different conditions were determined by a digital pH-meter. pH measurements were repeated for multiple emulsions after 1, 3, 7,14, 21 and 28 days of preparation.[17]

7. In vitro drug release study: The in vitro drug release study was carried out on a simple dissolution cell using cellophane membrane (thickness-200mm, breaking strength-2.7 kg/cm). Prior to release studies, the cellophane membrane was soaked in distilled water for 6 hours, washed frequently 4 times by changing distilled water, then immersed in 5% v/v glycerol solution for at least 60 min and washed finally with 5 portions of distilled water. 15 ml freshly prepared multiple emulsion was added to donor chamber, made up of a hollow

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glass tube (2.5 cm in diameter and 10 cm in length) and membrane was tied on bottom end of the tube with a nylon string.[19] This tube was dipped into 250 ml vessel containing 100 ml of PBS pH 6.8 and was stirred at 100 rpm on a magnetic stirrer and maintained at 37 °C which acted as receiving chamber. Aliquots of 1ml were collected from receiving chamber at predetermined time intervals and the drug content was determined on UV spectrophotometer at 287.6 nm after suitable dilution.[20]

RESULT AND DISCUSSION:

1. PREFORMULATION STUDIES:

1.1 Identification of Drug:

1.1.1 Organoleptic Characteristics:

Table No.1: Organoleptic Characters of Repaglinide

S.No.	Properties	Observation
1	Color	White
2	Odor	Odorless
3	Taste	Tasteless

1.1.1 Melting Point Determination:

The melting point of **Repaglinide** was found to be 126.8˚C.

Table No.2: Melting Point of Repaglinide

Drug	Observed
Repaglinide	126.8℃

1.1.2 UV Spectroscopy:

The maximum wavelength of Repaglinide was found to be 288 nm which matches the reported wavelength.

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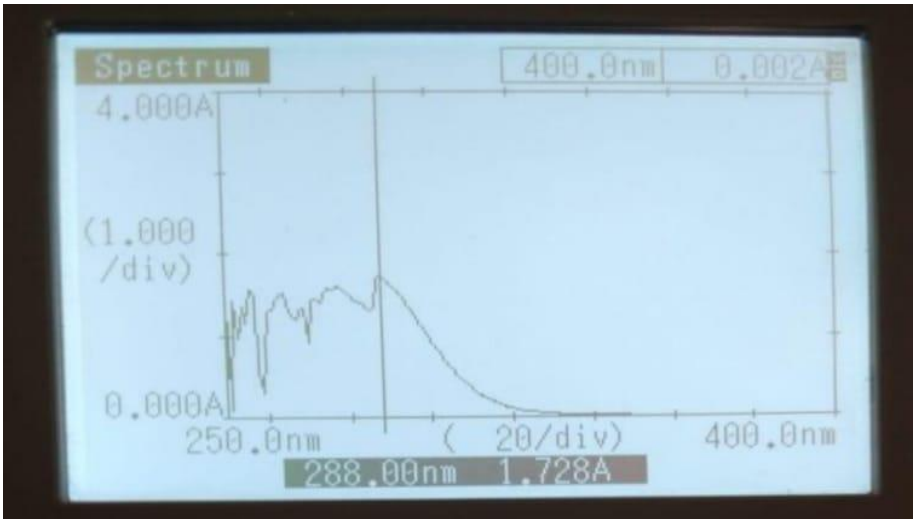

Fig no. 1: Spectrum of Repaglinide by UV Spectroscopy

1.1.3 Standard Calibration Curve:

A standard calibration curve for the drug was obtained by measuring maximum absorbance at 288 nm (λ max), and by plotting the graph of absorbance V/s concentration. Table shows the absorbance readings of repaglinide in 0.1 N HCl, and Phosphate buffer pH 6.8 between 5-25 µg/ml concentrations. The standard plots of Repaglinide are shown in graphs.

Calibration curve of Repaglinide with 0.1N HCl

Table no. 3: AbsorbancedataofRepaglinidein0.1N HCl for preparation of calibration curve, at 288 nm

S.No	Concentration µg/ml	AbsorbanceMean±StandardDeviation
01	05	0.203
02	10	0.412
03	15	0.612
04	20	0.812
05	25	0.974

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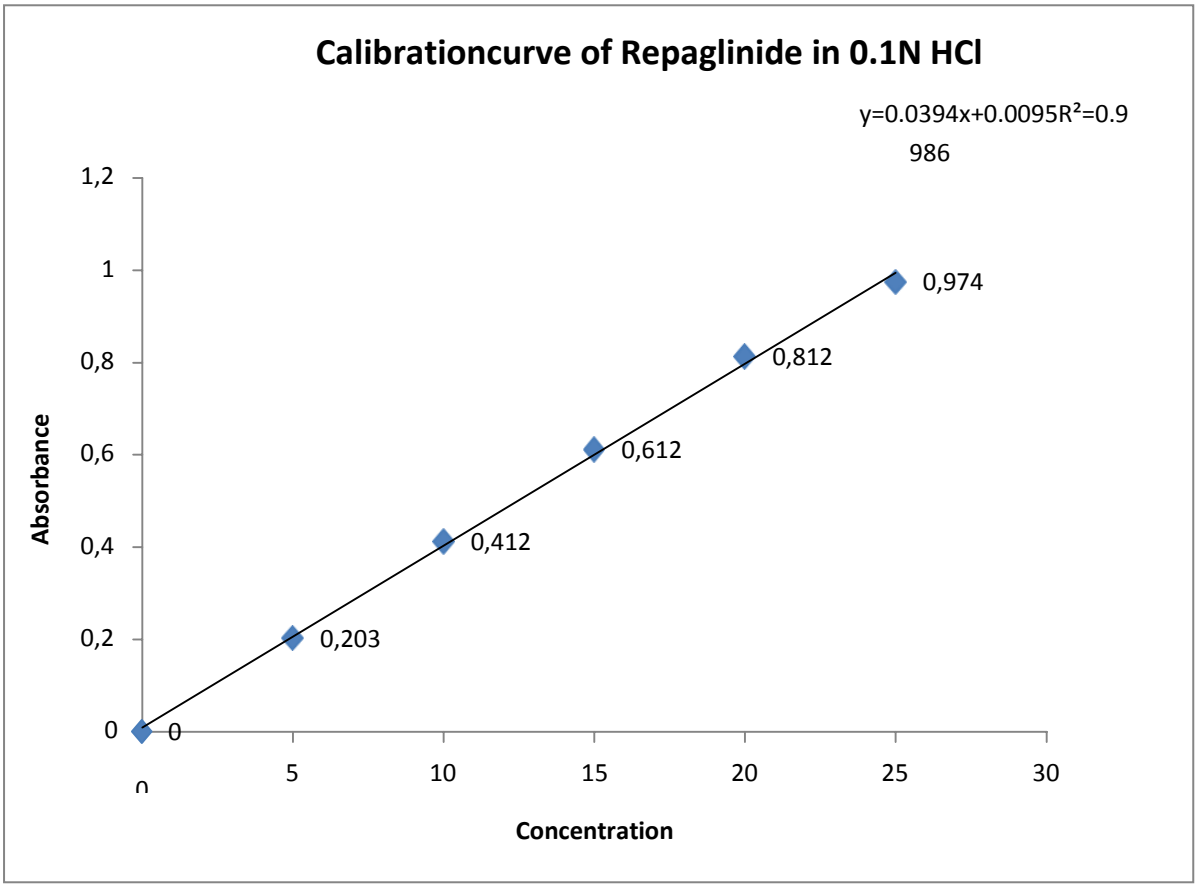

Fig no. 2 Calibration graph of Repaglinide in 0.1N HCl

Calibration curve of Repaglinide with Phosphate buffer pH 6.8

Table No. 4: Absorbance data of Repaglinide in phosphate buffer pH 6.8 for preparation of calibration curve, at 288nm

S.No	Concentrationμg/ml	AbsorbanceMean±StandardDeviation
01	05	0.264
02	10	0.583
03	15	0.810

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04	20	1.108
05	25	1.375

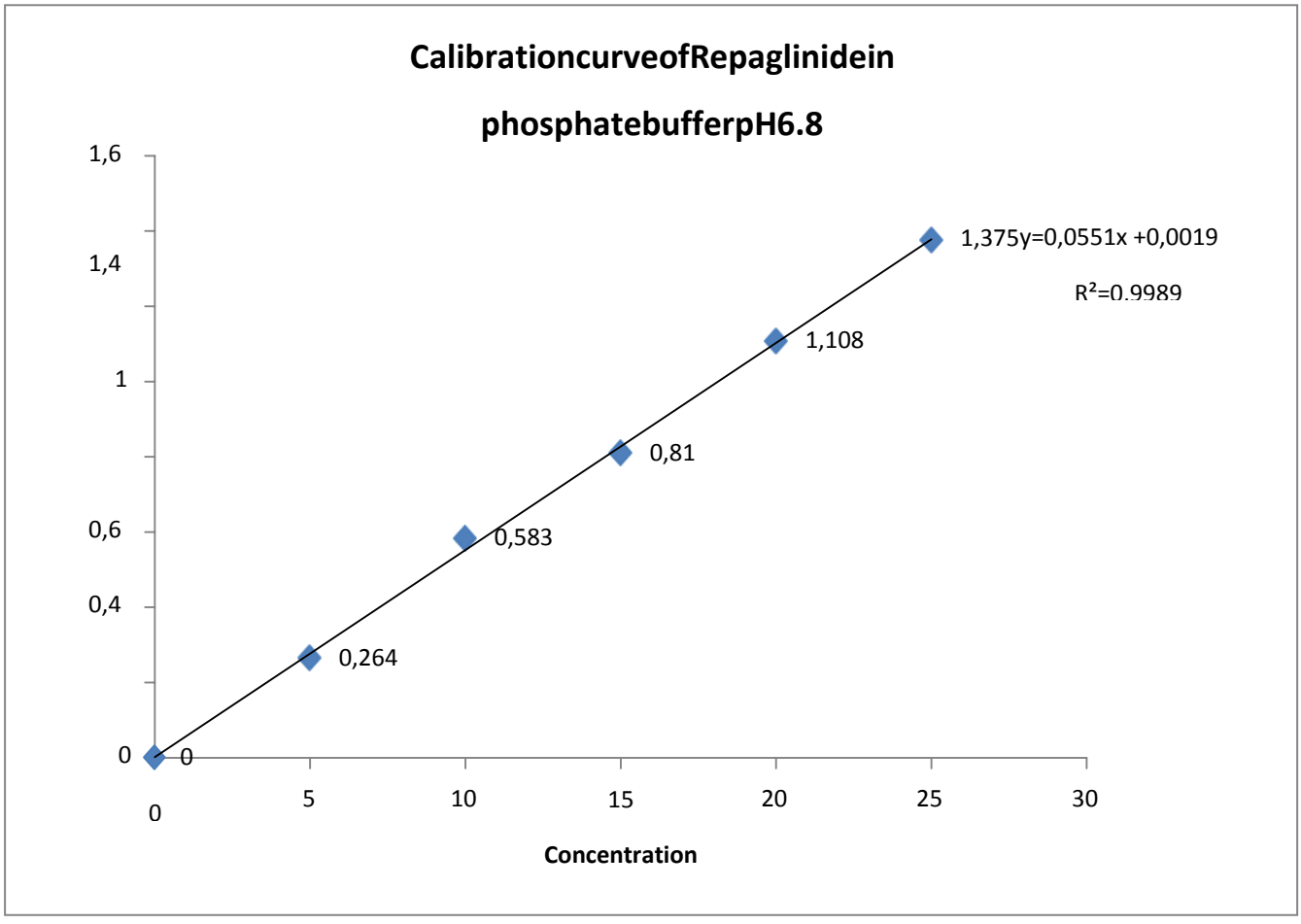

Fig. no. 3 Calibration curve of Repaglinidein phosphatebufferpH6.8

1.1.4 IR Absorption Spectrum:

The IR spectrum of drug substance was authenticated using IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted. Various peaks of the Repaglinide were shown in figure.

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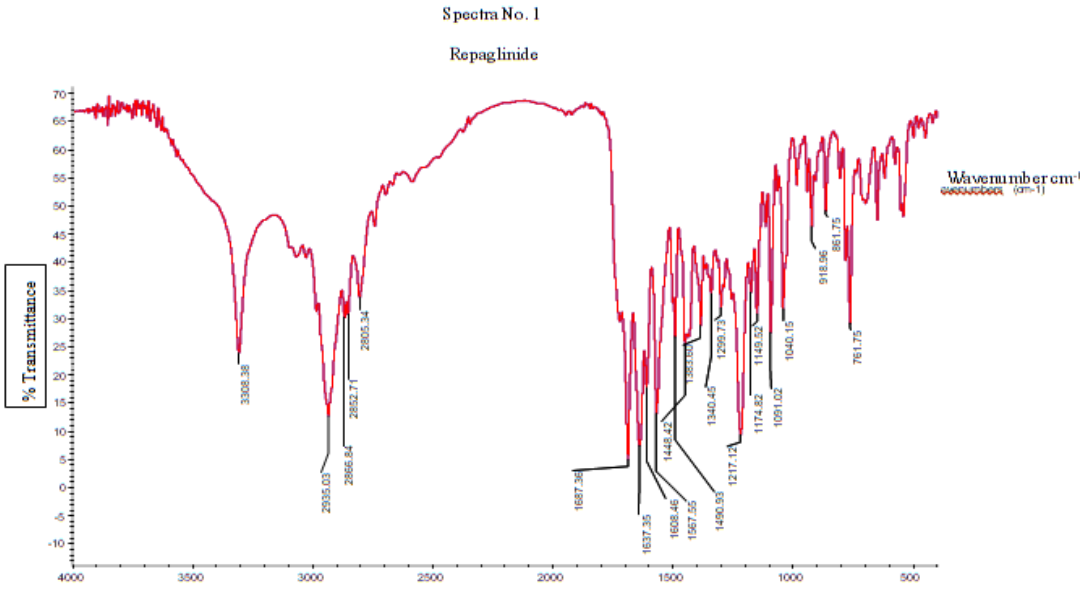

Fig no. 4 IR spectra of Repaglinide

The IR spectra of the drug, polymers and their combinations are shown in Spectra.
The characteristics absorption peaks of repaglinide were obtained at1687.3cm-1, 2935.03 cm-1, 1217.12 cm-1, and 3308.38cm-1. The IR spectras of the drug and polymer combinations were
compared with the spectra of pure drug and individual polymers. The principle peaks obtained for the combinations were almost similar to that of the drug.
The details of IR spectra are mentioned in Table.
The IR spectra of the Drug-HPMC, Drug –chitosan, and Drug-Sodium alginate, did not show any changes. The possibility of interaction was ruled out as there was no major shift in the absorption bands of drug and the formulations as shown in.

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Table No. 5: Comparison of I.R. Spectra of Repaglinide and in Combination with excipients

Sl. No.	System	C=O(cm^{-1})	C–H (cm^{-1})	--CH_3(cm^{-1})	N-H(cm^{-1})
1.	**Repaglinide (RPG)**	1687.36	2935.03	1217.12	3308.38
2.	**RPG- SPAN**	1687.39	2934.99	1217.75	3308.74

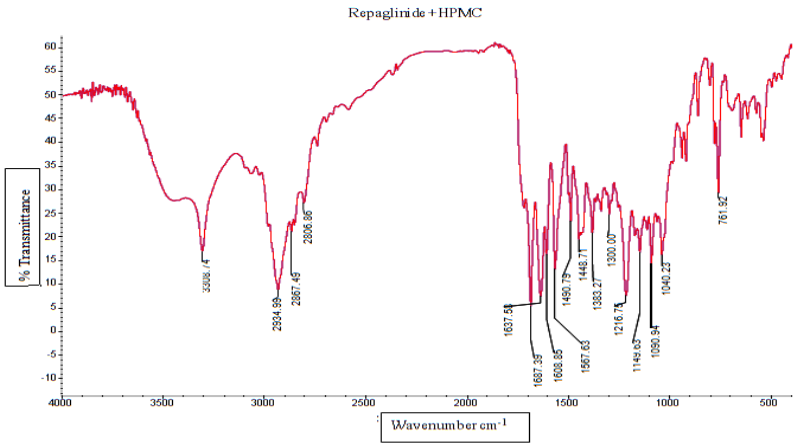

Fig no. 5 IR spectra of Repaglinide with Excipients

1.1.5 Determination of solubility of Repaglinide in various solvents:

Table no. 6: Solubility data of Repaglinide

S.No.	Solvent	Inference
1	Methanol	Freely soluble
2	Phosphate buffer 6.8	Soluble
3	Water	Poorly Soluble

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1.1.6 Determination of solubility of solid dispersion:

Table No. 7: Solubility data of solid dispersion

S.No.	Water	Solubility (mg/ml) Mean ± SD (n=3)	Inference
1	Pure drug	2.94 ± 0.11	Poorly Soluble
2	Drug- CD (1:3)	4.86 ± 0.12	Soluble
3	Drug- CD (1:4)	8.74 ± 0.15	Freely soluble

1.1.7 Drug Excipient Interaction Studies:

The drug Repaglinide was found to be compatible with various excipients which were selected for formulation of Multiple Emulsion. The compatibility was assessed by TLC and the retention factors of all ratios found similar.

Table No. 8: Data of drug-excipient interaction study.

S.No.	Drug/Drug + Excipient Ratio (1:1)	Initial appearance	Final appearance	Retention factor
	Drug (Repaglinide)	White Powder	White Powder	0.55
	Pure Drug + Span	Transparent white	Transparent white	0.53
	Pure Drug + Tween	Slightly Yellow	Slightly Yellow	0.56

2. FORMULATION AND DEVELOPMENT:

Table No. 9: Formulation batches of multiple emulsion of repaglinide

Formulation	F1	F2	F3
Repaglinide (mg)	100	100	100
Span 40 (gm)	0.6	0	0
Span 60 (gm)	0	0.6	0
Span 80 (gm)	0	0	0.6
Tween 80 (ml)	1	1	1

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Liquid Paraffin (ml)	14	14	14
Phosphate Buffer (6.8) (ml)	30	30	30

3. EVALUATIONS OF MULTIPLE EMULSIONS:

3.1. Globule size:

Table No. 10: Globule Size

Batches	Emulsifying Agents	Conc^{n}	Globule Size (µm)
F1	Drug, Span40, Tween80, Liq.Paraffin, Phosphate buffer	100mg, 0.6gm, 1ml, 14ml, 30ml	19.26
F2	Drug, Span60, Tween80, Liq.Paraffin, Phosphate buffer	100mg, 0.6gm, 1ml, 14ml, 30ml	12.47
F3	Drug, Span80, Tween80, Liq.Paraffin, Phosphate buffer	100mg, 0.6gm, 1ml, 14ml, 30ml	5.84

The data shows the formulation **F3** forms the good globule size.

3.2. Entrapment efficiency:

Entrapment efficiency of multiple emulsion shown in fig.

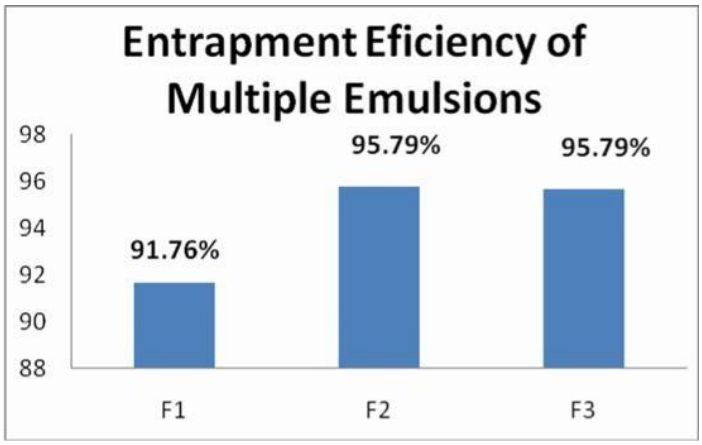

Fig no.6 Entrapment efficiency

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3.3. Stability tests:

The tests were performed on sample kept at 8 ± 0.1 ˚C (in refrigerator), 25 ± 0.1 ˚C (in oven), 40 ± 0.1 ˚C (in oven) and 40 ± 0.1 ˚C at 75% relative humidity (RH) (in stability cabin). The study showed that the formulations was stable for 28 days without any change at lower temperature conditions i.e. at 8 ± 0.1 ˚C (in refrigerator) and 25 ± 0.1 ˚C (in oven). But from 21 days the formulations kept at the elevated temperature i.e. 40 ± 0.1 ˚C (in oven) and 40 ± 0.1 ˚C at 75% relative humidity (RH) (in stability cabin) shows the signs of instability by the slight change in color which can be due to the oily phase separation which is promoted at elevated temperatures, increase in the pH and decrease in globule size from the 7 days which can be due to the expulsion of the internal droplets to external water phase and with the increase in phase separation.

3.4. Organoleptic characteristics of Multiple Emulsion:

Table No. 11: **Organoleptic characteristics**

Time	Liquefaction			Color			Phase separation			Centrifugation		
	A	B	C	A	B	C	A	B	C	A	B	C
0 hr	-	-	-	W	W	W	-	-	-	-	-	-
1 hr	-	-	-	W	W	W	-	-	-	-	-	-
24hr	-	-	-	W	W	W	-	-	-	-	-	-
72hr	-	-	-	W	W	W	-	-	-	-	-	-
7days	-	-	-	W	W	W	-	-	-	-	-	-
14days	-	-	-	W	W	W	-	+	-	+	+	+
21days	-	-	-	W	YW	YW	-	+	+	+	+	+
28days	-	+	+	YW	YW	YW	-	+	+	+	+	+

-=Nochange;+=slightchange; W=white;YW=yellowish-white;++=morechangeA =8^{o}C;B=25^{0}C;C =40^{0}C(in oven)(n = 3).

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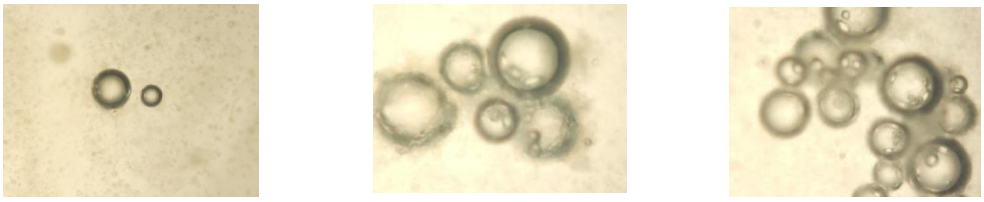
3.5. Microscopic tests:



F1 **F2** **F3**

Fig.no. 7 Microscopic image of F1, F2, F3.

3.6. In vitro drug release:

The result indicate more release of **F3formulation** will be higher release profile as compare to other formulation and data was shown in figure.

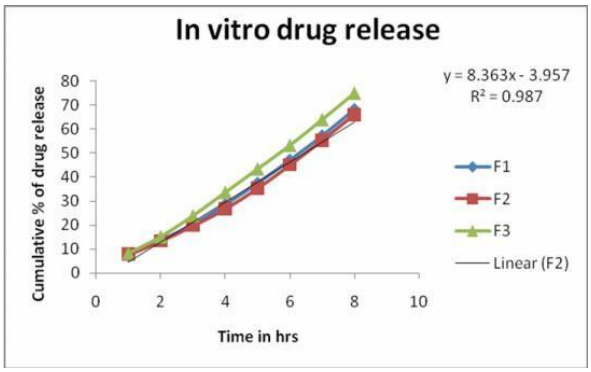


Fig.no.8 In-vitro drug release of multiple emulsions

SUMMARY AND CONCLUSION:

Repaglinide (Prandin) is an oral insulin secretagogue of the meglitinide class(Antidiabetic) of BCS Class IIhas low bioavailability. It is used to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood). The Multiple Emulsion is the complex polydispersed system in which an emulsion is incorporated in another emulsion therefore they are also known as "*Emulsion of Emulsion*". The aim was to prepare a stable Multiple Emulsion of Repaglinide by incorporating various hydophilic and lipophilic surfactants at different concentrations. The characterization of drug sample was done using spectrophotometric analysis and melting point determination. All the observations and recorded data were identical to the values reported in literature. Calibration curves of Repaglinide in 0.1N HCl and phosphate buffer (pH 7.4) were prepared using a double beam UV-visible spectrophotometer (Shimadzu 1800)The different formulations of multiple emulsion were evaluated on the basis of their

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