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Advances in Bioresearch

ORIGINAL ARTICLE

Development and Evaluation of Poorly Water Soluble Repaglidine Formulation using Hydrotropy

Vinod M. Thakare*., Sneha R. Chandewar., Maheshwari*
Department of Pharmaceutical Quality Assurance,
Dadasaheb Balpande College of Pharmacy, Nagpur
SGSITS, Indore
Corresponding Author's Email: vmthakre@gmail.com

ABSTRACT
Hydrotropy is suggested to be superior to other solubilization methods, such as miceller solubilisation, miscibility, co-solvency and salting in, because the solvent character is independent of pH, has high selectivity and dose not require emulsification. It only requires mixing the drug with the hydrotrope in water. In the present study it was clearly observed that Hydrotropic solubilization formulation can be effectively produced by processing via fusion method with enhanced solubility. Sodium oliate & Sodium caprylate combinations were optimized and stable HS systems were developed successfully. Drug content analysis and in vitro dissolution study of Repaglidine is most preferably used for solubility and dissolution enhancement than other drugs. FTIR studies shows there was no degradation of drug. The solubility studies showed there is a possibility of improved solubility. Analysis of X-ray diffraction showed that Repaglidine existed in the amorphous form within the Hydrotropic solubilization formulation fabricated using the solvent fusion method. Finally, it could be concluded that Hydrotropi solubilization of Repaglidine would improve the aqueous solubility.
Key words: *Repaglidine, Hydrotropy, Solublization, Fusion, Aqueous solubility.*

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INTRODUCTION

More than one-third of drug listed in the U.S Pharmacopeia fall into the poorly water-soluble or water insoluble categories. It is well known that drug efficacy can be severely limited by poor aqueous solubility. It is also known that the side effects of some drugs are the results of their poor solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficacy and/or reducing side effects of drug. This is true for parenterally, topically, and orally administered solutions [1]. In pharmaceutical sciences, solubility is commonly related to the bioavability of the compound of interest, especially for poorly soluble soluble compounds. Slow absorption rate result in an erratic and variable profile of drug level. Administration of a drug in any dosage form, except solution involves a dissolution step. Thus, it is required that the drug has to be present in the dissolved state at the site of absorption and then only it can be absorbed. In general, in order for a drug to exert its biological effect, it must be soluble in and transported by the body fluids, transverse the required biologic membrane barriers, escape widespread distribution to unwanted areas, enduremetabolic attack, penetrate inadequate concentration to the sites of action and interact in a specific fashion, causing an alternation of cellular functions [2]. Factor Affecting The Solubility ie. nature of solute and solvent, Particle size, Molecular size , Temperature. Methods to enhance the solubility of drug [3-5]. Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in the formulation of dosage forms of water insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the side effects (in place of using a large concentration of one hydrotrope a blend of, say, 5 hydrotropes can be employed in 1/5th concentrations

reducing their individual toxicities [6]. Hydrotropic agents are ionic organic salts. Additives may either increase or decrease the solubility of a solute in a given solvent. The salts that increase solubility are said to 'salt in' the solute and those salts that decrease the solubility 'salt out' the solute. The effect of an additive depends very much on the influence; it has on the structure of water or its ability to complete with the solvent water molecules [7-9].

MATERIAL AND METHODS

In the preparation of hydrotropic solubalization and evaluation following chemicals and reagents were used ie. Repaglidine was obtained from Enaltech Pharmaceuticals, Mumbai. whereas Sodium oliate, Sodium caprylate, Microcrystalline cellulose, Starch, Magnesium stearate, Talc , Sodium starch glycolate were laboratory grade and purchased from loba chemicals, Mumbai.

Identification of drug [10-13]

Identification of Repaglidine was carried out by melting point determination, differential scanning calorimetry (DSC), and fourier transform infra- red spectroscopy (FTIR).

High performance liquid chromatograohy

A stock solution of REG(1000µG/ml) was prepared in acetonitrile. Working standard solutions of RGE (10-50µG/ml) were prepared by suitable dilution of the stock solution with mobile phase each drug solution (20µl) was injected for HPLC determination of peak area and retention time [14].

Standard calibration curve and verification of λ max:

It involves the measurement of the amount of the ultra violet (190-380nm) or visible (380-800 nm) radiation absorbed by a substance in solution [15-16].

Calibration curve in Acetate buffer pH 5

Accurately weight repaglidine was dissolved in 100 ml of Acetate buffer pH 5 (100 µg/ml) stock solution of drug was prepared in Acetate buffer pH 5 and suitable dilutions were made and scanned at λ max 283 nm. [17-18]

Saturation solubility study

Repaglidine selected in the present work is having poor aqueous solubility characteristics. Physical mixture of Repaglidine and sodium oliate, sodium caprylate was added into glass-stopper flasks containing 10 ml of water of increasing concentrations of sodium oliate,sodium caprylate and in physical mixture ratio(Drug: Sodium oliate:Sodium caprylate) (1:0:0, 1:1:1, 1:2:1, 1:3:1). The flasks were sealed and shaken on rotary shaker at room temperature. After equilibration for 96 hr. the solutions were filtered through Whatman filter paper. Then the filtrates were estimated by UV spectroscopy at. 241 nm [19].

Preparation of Physical Mixture

The various techniques were tried and performed on the trial and error basis with best results and feasibility we choose melt technique. The physical mixture of Repaglidine with sodium oliate was prepared by mixing the required amount of Repaglidine and hydrotrope in 1:1:1, 1:2:1 and 1:3:1 ratios for 15 min in a mortar with the help of pestle until a homogeneous mixture was obtained. This resulting mixture was sieved through a 80# mesh screen [20].

Preparation of Hydrotropy Solubilization

Hydrotropic solubilization of Repaglidine were prepared by melt/ fusion method using sodium oliate & sodium caprylate in various w/w ratios. Sodium oliate & sodium caprylate was placed in a porcelain dish and allowed to melt by heating above the melting point of carrier with continuous stirring until homogenous dispersion was obtained. For rapid solidification, the resultant solution was cooled in ice bath and, it was then scrapped, pulverized and passed through sieve [21-22]. The ratio was Repaglidine, Sodium oliate and Sodium caprylate, 1:1:1, 1:2:1 and 1:3:1 by using the Fusion method.

Percentage yield (%)

Percent production yield was calculated to determine % yield or efficiency of any method thus it is helpful in the selection of appropriate method of production. Hydrotropic solubilization was collected and weight to determine production yield [23].

Determination of drug content

Accurately weight hydrotropic solubilization equivalent to 10 mg of Repaglidine was transfer to 10 ml of volumetric flask containing 10 ml of methanol and dissolved. 1 ml of this solution was diluted to 10 times with methanol and absorbance was measured at 241 nm [24].

Evaluation of powder

Angle of repose:

Angle of repose was determined to find out the flow properties of drug [25].

Bulk Density:
It is the ratio of total mass of powder to the bulk Volume of Powder It is expressed in gm/ml [25].
Tapped Density:
It is the ratio of total mass of powder to the tapped volume of the powder. Volume was measured by tapping the powder [25].
Compressibility index and Hausner's ratio
The compressibility index and Hausner's ratio are determined by measuring both bulk density and the tapped density of a powder.[26]
Formulation of Repaglidine Tablet
On the basis of trial and error, we prepared total 25 formulation and from the disintegration, dissolution results we choose 10 formulations for further study. The raw materials passed through a screen (# 80). Repaglinide hydrotopic mixture was taken to the equivalent amount of pure 10 mg repaglinide, and then mixed with other excipients. Compressed the tablet by tablet rotary punching machine [27].
Post Compression study
For the evaluation purpose 10 batches were selected on the basis of Disintegration time & Dissolution & Hardness test and drug release.
Weight variation test as per USP
For weight variation test we followed as per USP protocol [28-29].
Hardness
The tablet should be holds between the two anvils apply the force and breaking of tablet is noted. Six tablet from each batch were taken [30].
Friability
Six tablet were accurately weighed and placed in friability test apparatus, then revolved it at 25 rpm \ for 4 min. After de-dusting, the friability was calculated by using the formula [31].
Disintegration test as per USP
The disintegration test was carried out using the disintegration test apparatus USP [30].
Dissolution studies as per USP
Dissolution studies were carried out using USP type II (paddle apparatus) at 75rpm pH 5 acetate buffer was used as dissolution medium. Temperature was maintained at 37 ±0.5 0C. Aliquots of dissolution media was withdrawn at specific time intervals and it was filtered. Same quantity of fresh media was replaced. The filtered solution was used to determine the estimation of drug content. The absorbances were measured at 283 nm by UV/Visible spectophtometer. The test was carried out for 30 minutes [31].
Accelerated Stability study
The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The stability studies were carried out at different protocol as per ICH guidelines.
Following conditions were applied during accelerated stability studies

- 25^0C/60% RH analyzed at a time interval of 30 days till a period of 90 days.
- 40^0C/75% RH analyzed at a time interval of 30 days till a period of 90 day

Deterioration of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity [32, 33].

RESULTS AND DISCUSSION:
Preformulation study
Physical Appearance
The drug was physically identified by visual examination and sensory nerves for colour and odour parameter and complies with the standards.
Melting point of Repaglidine
The melting point of Repaglidine was found to be 128^0C which was same as reported in literature ($128^0 \pm 2^0$C).
Selection of λmax
Wavelength of maximum absorbance (λmax) for the solution of Repaglidine prepared in distilled methanol was found to be at 241 nm which was concordant with given literature. The spectrum of Repaglidin is shown in figure 1.
Fourier Transform Infra Red Spectroscopy(FTIR) Drug
Fourier transform infra-red spectroscopy has been used to assess the interaction between carrier and drug molecule. The FTIR spectrum of Repaglidine showed in fig no 2 and std. repaglidine FTIR was

showed in fig no 3. There was no considerable change in the positions of characteristic absorption bands and bonds of various functional groups present in the drug. This observation clearly suggests that the drug remains in its normal form with no prominent change in its characteristics.

Differential Scanning Calorimetry (DSC) Drug

The thermal analysis of drug were studied using differential scanning calorimetry (DSC) shown in Figures no.9-11. . Repaglidine have shown melting sharp endotherm at 136.49^{0}C. Whereas, disappearance of drug peak in the formulation indicates complete encapsulation of drug within the polymeric membrane.

The analysis of drug by X-ray Diffractometry (XRD)Drug

X-ray powder diffraction was conducted to clarify the physical nature of Repaglidine Figure no. 11-13 shows the diffraction pattern of optimum formulation respectively. Pure Repaglidine showed sharp peaks intensities in the region 6-27^0 of 2Ø, demonstrating crystalline state of Repaglidine. The crystalline feature of Repaglidine in the optimum formula was significantly distorted.

Calibration curve of Repaglidine in acetate buffer pH5.

The calibration curve was plotted in acetate buffer having pH 5 and it was comparable to standard observations as showed in fig no. 16

Saturation solubility study

Hydrotropy technique showed significant improvement in the aqueous solubility of Repaglidine. Incorporation of Hydrotropes like sodium oliate, sodium caprylate enhances wettability of Repaglidine by the process of hydrophilization and may increases the aqueous solubility of Repaglidine as shown in Table No 2.

Fourier Transform Infra-Red Spectroscopy (FTIR) hydrotrope and physical mixture

There was no considerable change in the positions of characteristic absorption bands and bonds of various functional groups present in the drug, hydrotrope and physical mixture. This observation clearly suggests that the drug remains in its normal form with no prominent change in its characteristics even in its hydrotrope. It showed that Repaglidine was compatible with hydrotropic solubilization of melting method sodium oliate, sodium caprylate in various ratios as shown in Fig. No 6-8.

Differential scanning calorimetry (DSC) Hydrotrope and physical mixure

The result of DSC thermogram hydrottrope sodium oliate, sodium caprylate and mixture pf hydrotrope was showed in figures no 9-11. It shows respective endothermic peak at. 233.77^{0}C. Thermogram of physical mixture shows respective endothermic peak at 134^{0}C . Disappearance of drug peak in the formulation indicates complete encapsulation of drug within the polymeric membrane.

X-ray powder diffraction (X-RD) Hydrotrope and physical mixure

X-ray powder diffraction was conducted to clarify the physical nature of sodium oliate, sodium caprylate and physical mixture. Figure 12-14 shows the diffraction pattern of optimum formulation respectively. Hydrotrope showed high peaks intensities in the region 6-27° of 2Ø, demonstrating crystalline state of Repaglidine. Sodium oliate& sodium caprylate also showed crystalline structure in the diffraction spectra. The improvement in solubility of Repaglidine to the existence of Repaglidine the crystalline state.

High performance liquid chromatography(HPLC)

The calibration curve was plotted and showed in Fig. No 14.

Percentage yield (%)

Hydrotropic solubilization was collected and weight to determine production yield. Production yield of hydrotropic solubilization was found to be between 89.41 - 91.66 %.

Drug content determination:

Drug content of hydrotropic solubilization was found to be satisfactory in all batches. The ratio 1:1:1 (in hydrotropic mixture by melting methods) contain higher percentage of drug because of less quantity of hydrotrope and the ratio of 1:3:1 contain less percent of drug because of three times more quantity of hydrotrope in formulation.

Evaluation of Tablet

Hardness was found to be not more than 3.5kg/cm^2 and Disintigration time was found to be not more than 30 sec. It was concluded that all batches were in the range. All the test were pass by the formulations as shown in Table. No. 5.

% *In-vitro* dissolution of Tablet in pH 5 Acetate buffer

The % release of drug in Acetate buffer pH 5 was shown in Fig No. 16.

Accelerated Stability Studies

Optimized formulation (f1) was subjected to stability at 40^{0}c± 2^{0}c/75% RH ±5 % for 90 days. The product was evaluated for appearance and hardness, friability, disintegration. Drug release studies were conducted as per the planned scheduled.

Stability parameters of formulation F-1 stored at 40^{0}C+2^{0}C/75% ± 5

All results complies with the stability condition

In-vitro Dissolution study

It was done as per procedure given in material and method part. The results were illustrated in following table no. 7 Storage Condition at 40^{0}C ± 2^{0}C.The results were illustrated in following table no.6. The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable.

Table No.1: Composition of Tablet

Sr. No	Materials	F1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
1.	Repaglidine(S.D)(mg)	10	10	10	10	10	10	10	10	10	10
2.	Microcrystalline cellulose)(mg)	70	72	68	74	76	64	62	78	80	65
3.	Starch(mg)	10	8	12	6	4	16	18	2	-	15
4.	Magnesium Stearate (mg)	1	1	1	1	1	1	1	1	1	1
5.	Talc(mg)	20	20	20	20	20	20	20	20	20	20
6.	Aerosil(mg)	2	2	2	2	2	2	2	2	2	2
7.	Sodium starch glycolate(mg)	12	12	12	12	12	12	12	12	12	12
8.	Cross cormellose sodium(mg)	25	25	25	25	25	25	25	25	25	25

Total weight of tablet=150 mg

Table No.2 Saturation solubility study

Sr no	Physical mixture ratio	Distilled water(mg/ml)	Acetate buffer pH 5(mg/ml)
1	1:0:0	0.040	0.052
2	1:1:1	0.120	0.130
3	1:2:1	0.170	0.185
4	1:3:1	0.210	0.227

* Value expressed as Mean ±SD, n=3

Table No. 3. Yield of hydrotropic solubilization

Formulation code	Production yield (%) [?][?]HS(Hydrotropic Solubilization)
FM 1:1:1	82±0.02
FM 1:2:1	87.33±0.05
FM 1:3:1	89.41±0.03

* Value expressed as Mean ±SD, n=3

Table No.4. Drug content

Formulation code	% Drug content
FM 1:1:1	83.29 ±0.03
FM 1:2:1	87.72 ±0.05
FM 1:3:1	92.18 ±0.07

* Value expressed as Mean ±SD, n=3

Table No. 5 Average Repaglidine content, average weight and disintegration time of Repaglidine tablet.

Sr No	Formulation code	Average weight of tabs(mg)	Weight variation (mg)	Hardness (kg/cm^2)	Friability	Drug content	Disintegration time(sec/min)
1	f-1	150 mg	149.9±0.20	2.5±0.10	0.73	95.90±0.06	15 sec±2.3
2	F-2	150mg	148.2±0.21	2.2±0.09	0.73	98.89±0.09	17sec±1.5
3	F-3	150mg	150±0.19	2.4±0.15	0.75	97.97±0.07	20 sec±2.5
4	F-4	150mg	149.8±0.18	2.2±0.12	0.72	96.99±0.06	21 sec±2.8
5	F-5	150mg	146±0.21	2.3±0.15	0.71	94.98±0.05	20sec±2.4
6	F-6	150mg	148±0.19	2.1±0.18	0.69	96.89±0.06	19sec±2.6
7	F-7	150mg	151±0.18	2.0±0.16	0.70	97.90±0.07	25sec±2.9
8	F-8	150mg	147±0.19	2.2±0.13	0.67	96.99±0.06	24sec±2.7
9	F-9	150mg	148±0.21	2.4±0.15	0.69	94.98±0.05	20sec±2.5
10	F-10	150mg	149±0.20	2.1±0.13	0.71	98.99±0.09	25sec±2.9

* Value expressed as Mean ±SD, n=3

Table No.6. Accelerated stability study

Sr.No.	Parameter	Initial 0 days	30 days	60 days	90 days
1	%Friability	0.73±	0.72±	0.73±	0.74±
2	Hardness(Kg/cm²)	2.5±0.10	2.3±0.09	2.4±0.08	2.5±0.10
3	Drug Content(%)	95%±0.06	94%±0.05	94%±0.05	95%±0.06
4	Invitro Disintegration time(Sec)	15sec±2.3	15sec±2.2	20sec±1.5	15sec±2.3

* Value expressed as Mean ±SD, n=3

Table No.7 In- vitro dissolution study during accelerated stability study

Formulation (F-1)	Percentage Drug Release After 10 minutes			
	Initial(0Days)	30 Days	60 Days	90 Days
	94%±0.56	93%±0.43	92.5%±0.39	92%±0.56

* Value expressed as Mean ±SD, n=3

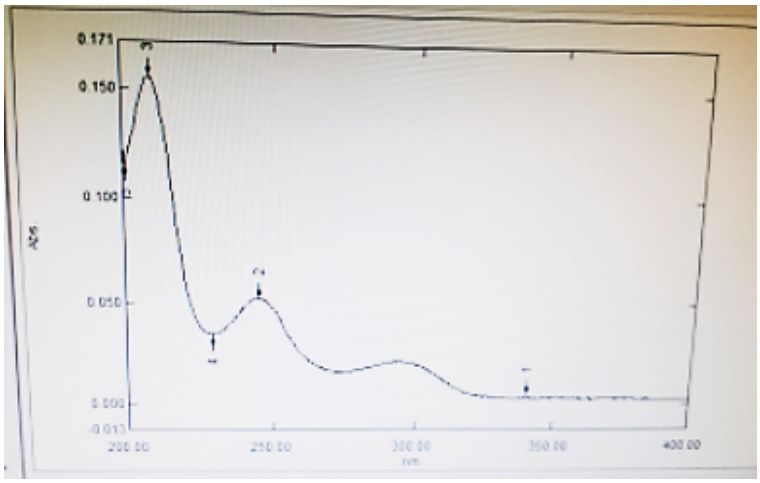

Figure 1: UV Spectrum of Repaglidine

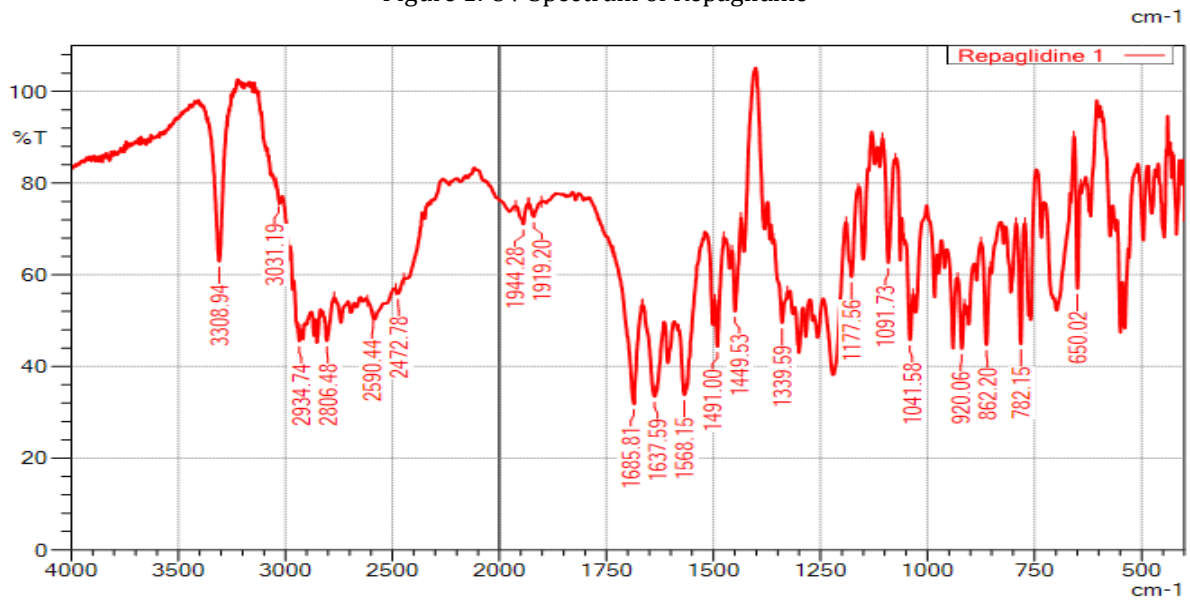

Fig. No 2. FTIR spectroscopy of API

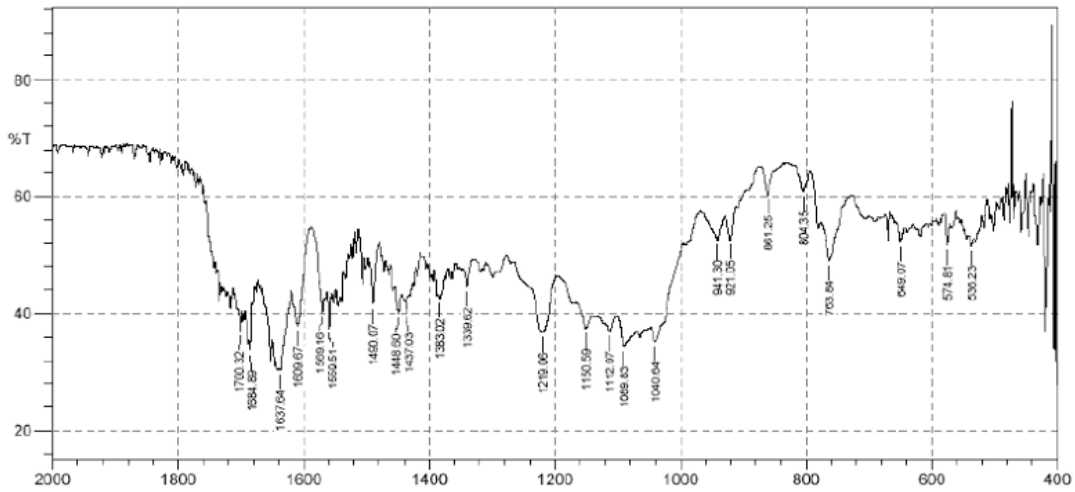

Fig. No 3. FTIR spectroscopy of standard API

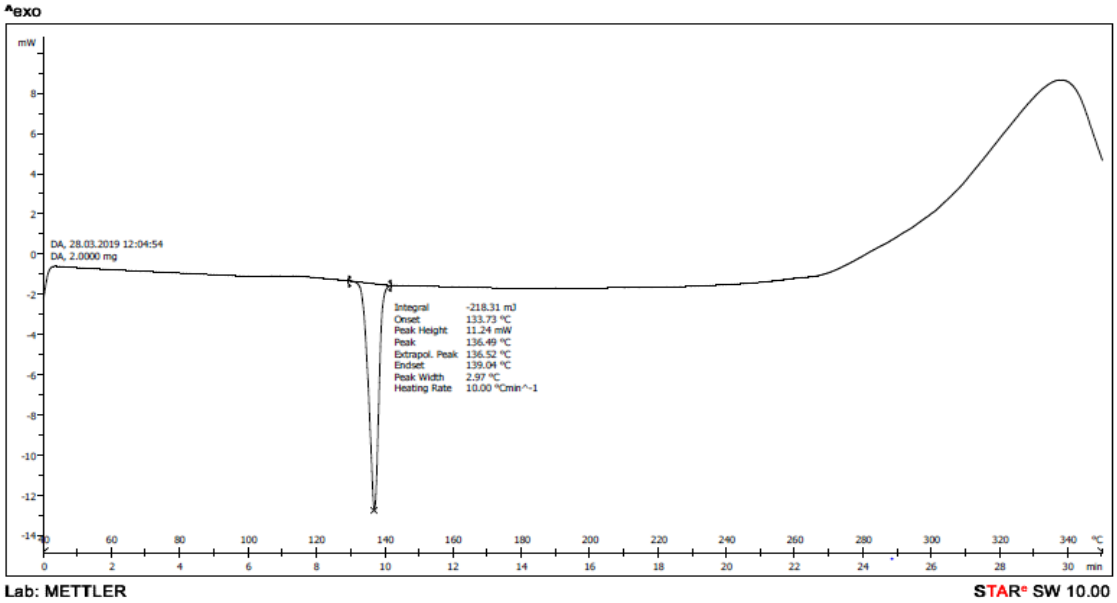

Figure No. 4 DSC Thermogram of Repaglidine

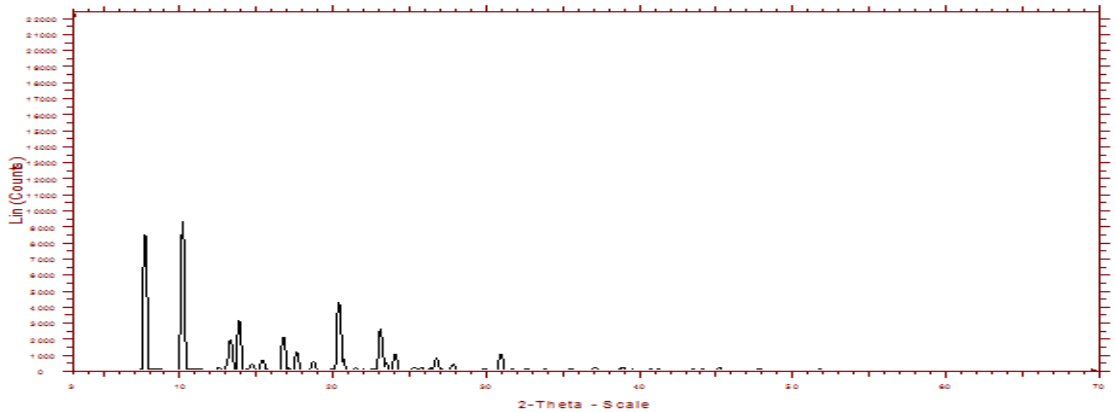

Figure No. 5 X-RAY Diffraction of Repaglidine

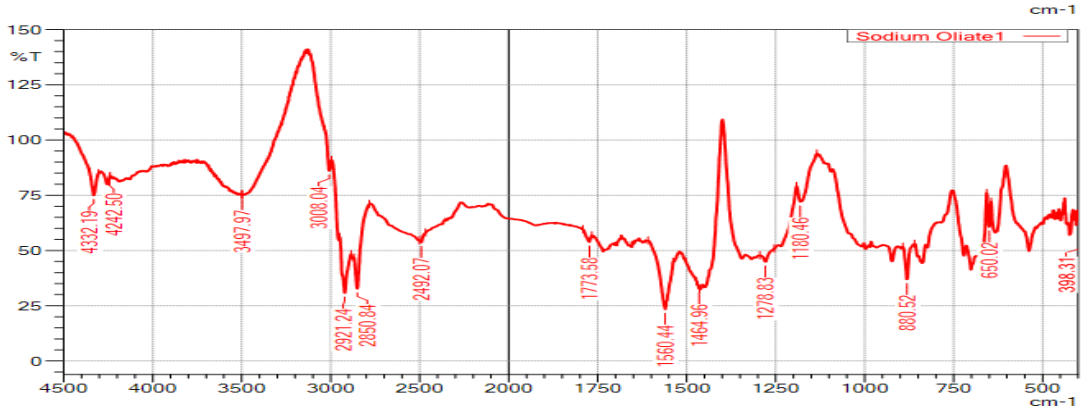

Figure No. 6. FTIR spectrum of Hydrotrope(sodium oliate)

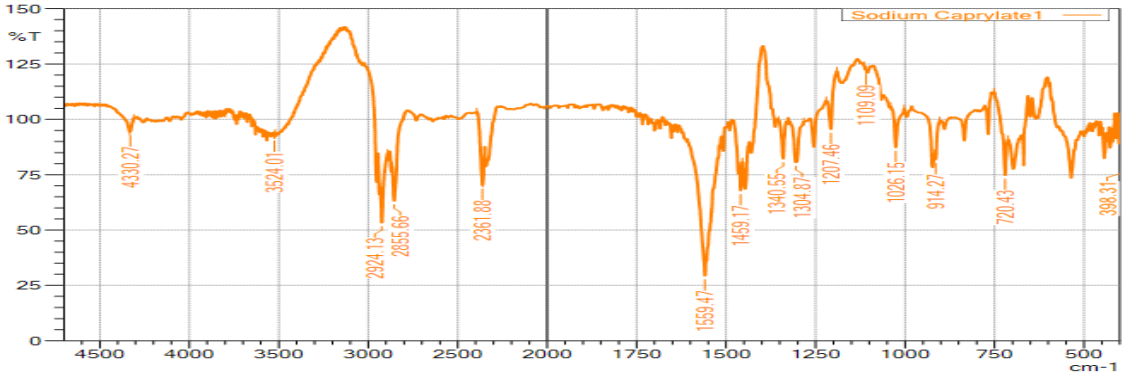

Figure No.7. FTIR spectrum of Hydrotrope(sodium Caprylate)

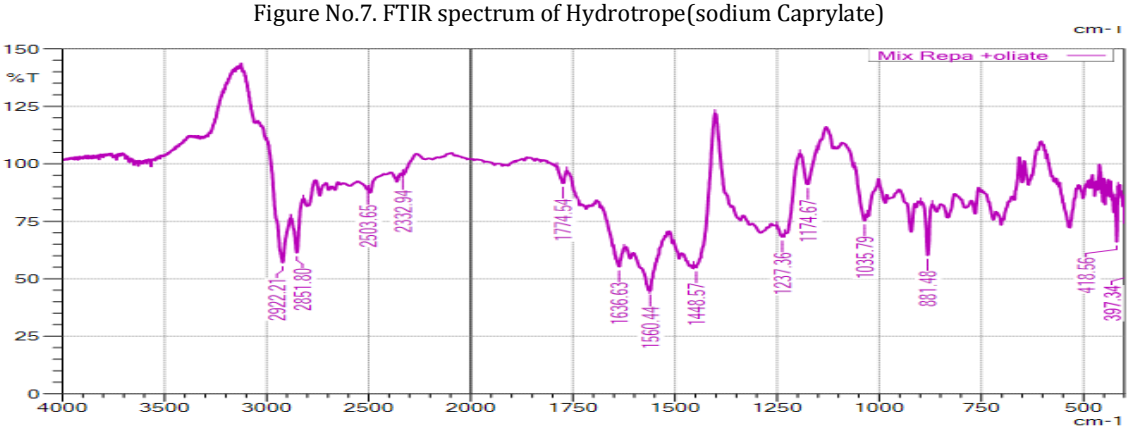

Figure No. 8 FTIR spectrum of physical mixture (Drug + hydrotrope)

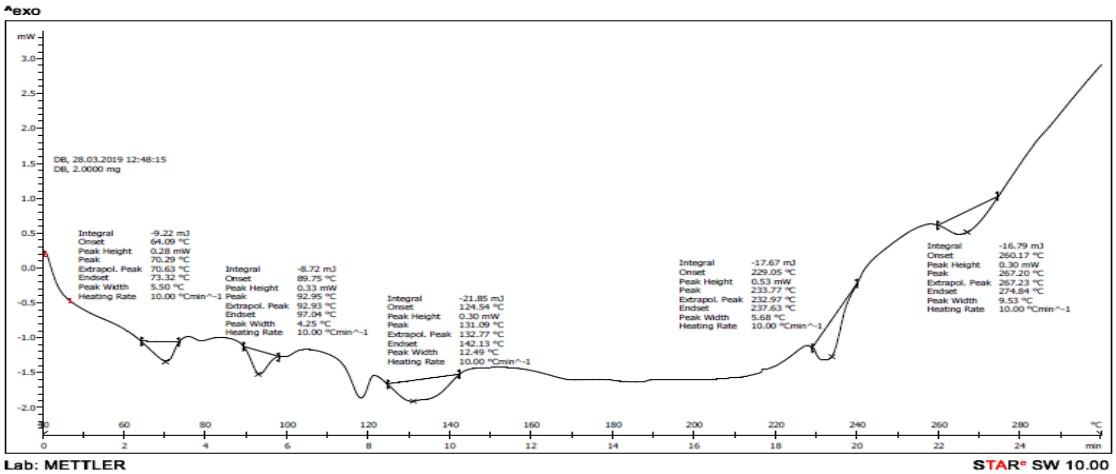

Figure No.9 DSC Thermogram of sodium oliate

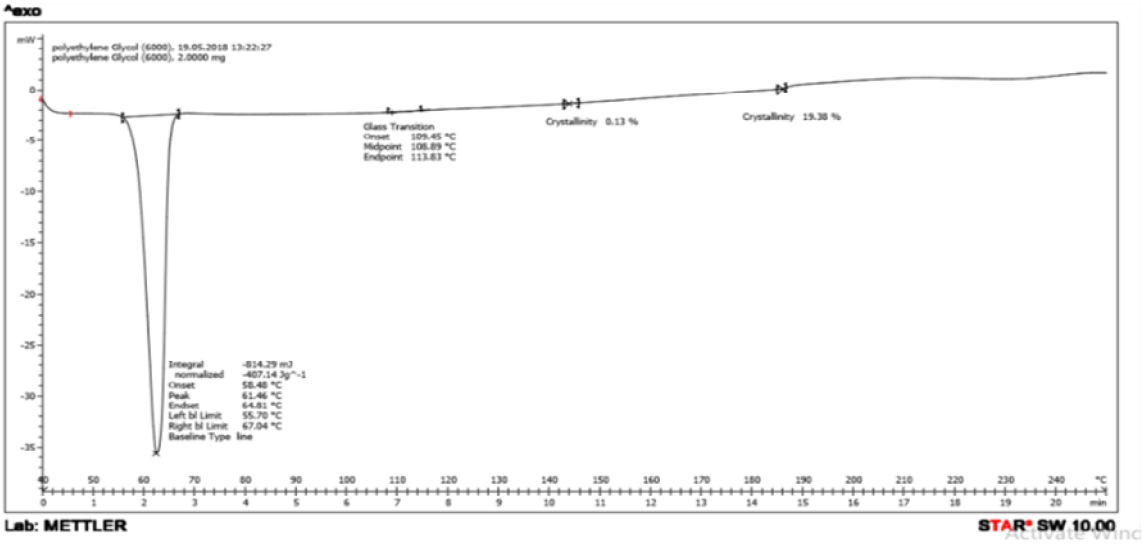

Figure No.10 DSC Thermogram of sodium caprylate

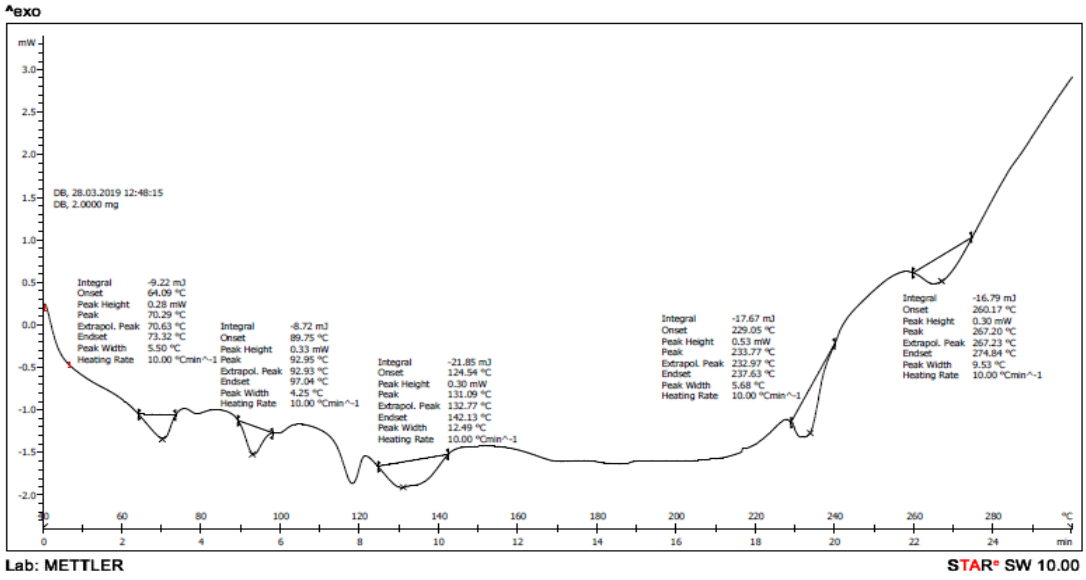

Figure No.11 DSC thermogram of Drug+ sodium oliate +sodium oliate+sodium caprylate

The analysis of hydrotrope and hydrotropic solubilization by X-ray Diffractometry (XRD)

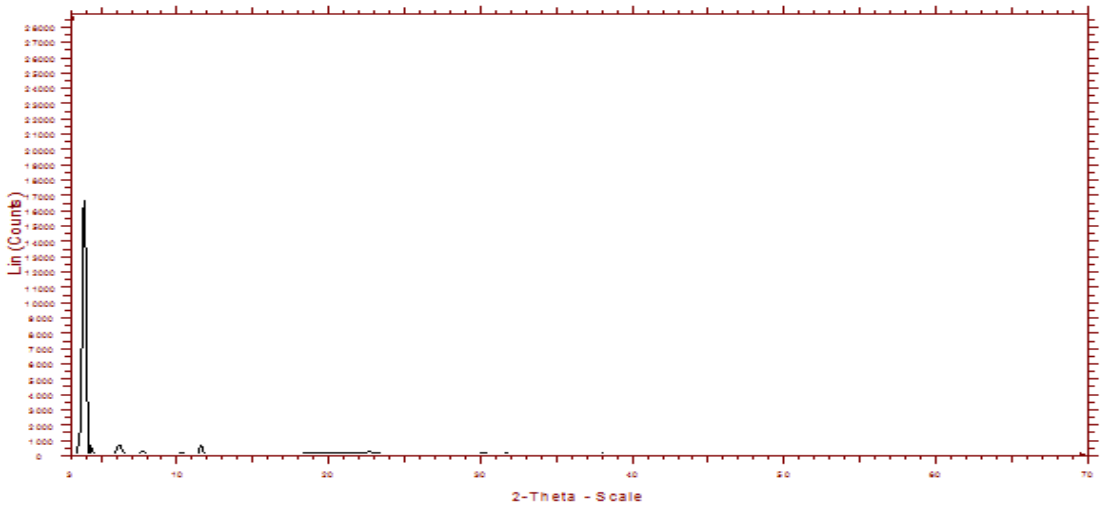

Figure No. 12 X ray Diffractogram of sodium oliate

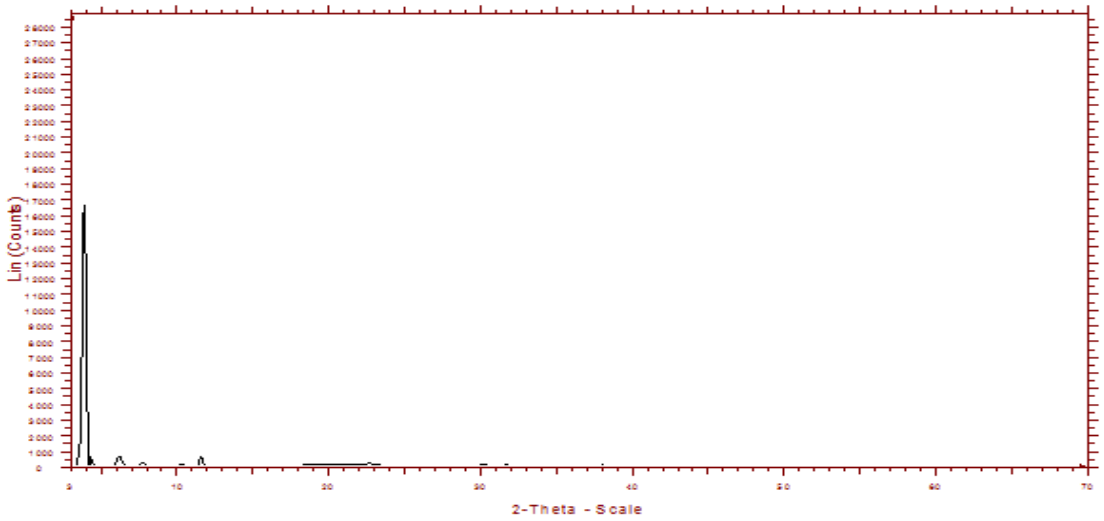

Figure No. 13 X Ray Diffractogram of sodium caprylate

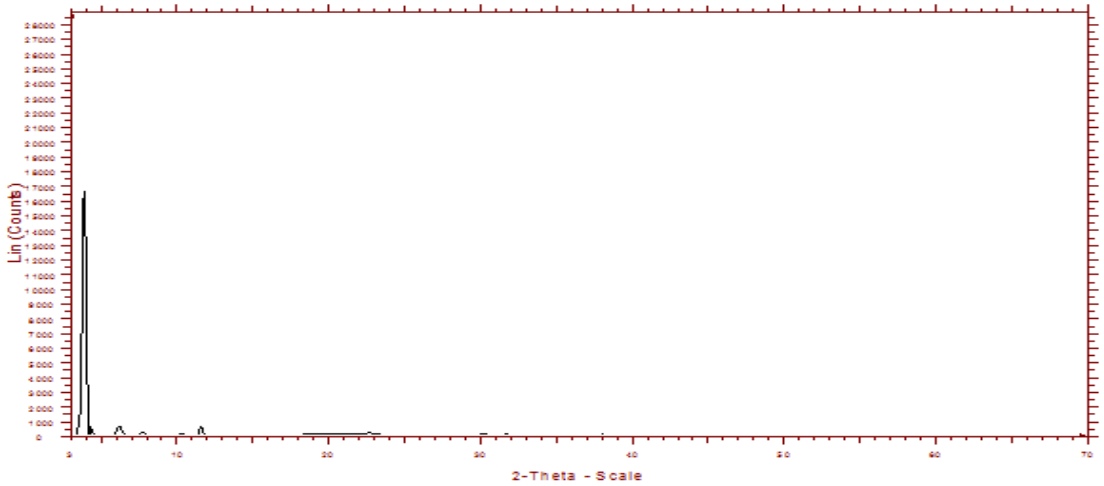

Figure No.14 XR Diffractogram of Drug+ sodium oliate +sodium oliate+sodium caprylate

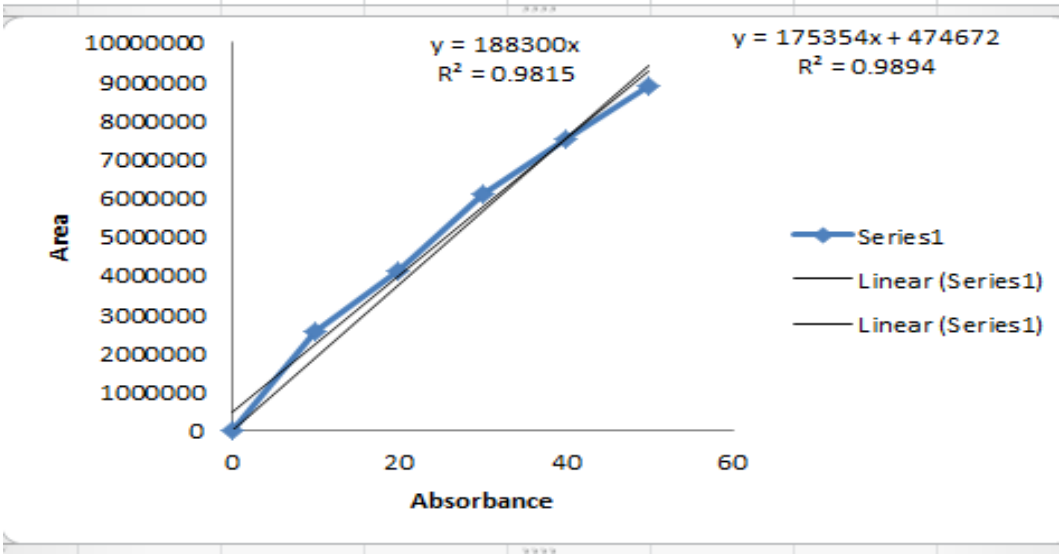

Fig.No.15. HPLC curve of Repaglidine

Calibration curve of Repaglidine in Acetate buffer pH 5

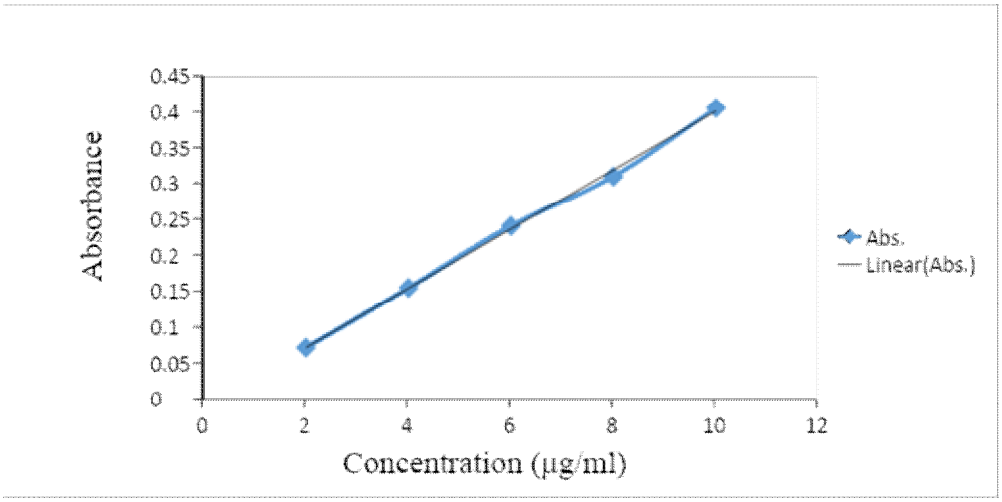

Figure No.16 Calibration curve of Repaglidine in Acetate buffer pH 5.

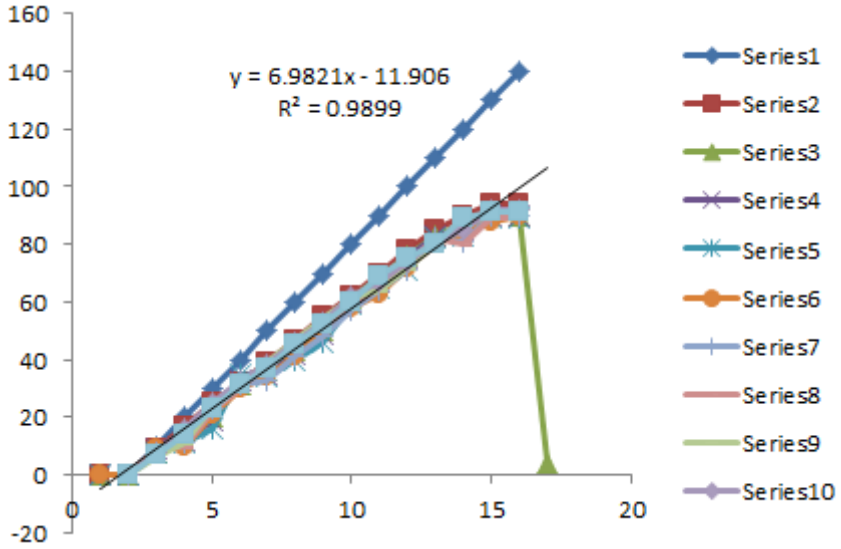

Figure No. 17. Cumulative % drug release from tablet in pH 5Acetate buffer

CONCLUSION

The prime aim of this project is to enhance the solubility of Repaglidine through easy and inexpensive methods in hydrotropic solubilization named fusion method . Different formulations with different ratio of hydrotrope were used. Percentages of drug release of each formulation were calculated. From this study it was concluded that fusion method was simple and effective methods for hydrotropic solubilisation for increase in solubility. The present study was carried out to investigate the utility of the sodium oliate and sodium caprylate in hydrotropic solubilzation of repaglidine (fusion method). All the preparations in fusion method showed better drug dissolution than that of pure drug within 1 hr. The fusion method may increased the solubility of the repaglidine in aqueous medium. Therefore, the percentage of drug release showed better dissolution within 1hr.

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