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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE CAPSULE OF REPAGLINIDE BY LIQUI-SOLID COMPACT METHOD

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ABSTRACT

Repaglinide belongs to class II drug in BCS classification i.e. low solubility and high permeability. Repaglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Conjugation of Repaglinide with the different types of carriers to increases the solubility and dissolution rate of Repaglinide. By increasing the solubility of Repaglinide, its bioavailability is increased. Capsule were prepared by using Repaglinide along with solvent (PEG 400), coating material (Aerosil), carrier (Avicel pH 102). The flow property of granules was found to be good for the all formulations. The in vitro dissolution time was found to be 100% in 12min for the formulation RIC9.

KEY WORDS

Repaglinide, Antihyperglycemic agent, PEG 400, Avicel, Aerosil

INTRODUCTION:

The oral route of drug administration is the route of choice for the formulators and continues to dominate the area of drug delivery technologies. However, though popular, this route is not free from limitations of absorption and bioavailability in the milieu of gastrointestinal tract. Whenever a dosage form is administered orally, drug in the dosage form is released and dissolves in the surrounding gastrointestinal fluid to form a solution. This process is solubility limited. Once the drug is in the solution form, it passes across the membranes of the cells lining the gastro-Intestinal tract. This process is permeability limited. Then onwards the drug is absorbed into systemic circulation. In short, the oral absorption and hence bioavailability of drug is determined by the extent of drug solubility and permeability[1,2.]

Solubility is defined as the maximum quantity of a substance that can be completely dissolved in a given amount of solvent[3,4]. The solubility of a substance becomes especially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance. The descriptive terms of solubility[6], that is expressed in units of parts of solvent required for each part of solute are given in Table 1.

Table 1. Descriptive terms of solubility

Description term	Parts of solvent required for 1 part of solute
Very soluble	solubility< 1
Freely soluble	1 < solubility< 10
Soluble	10 < solubility < 30
Sparingly soluble	30< solubility < 100
Slightly soluble	100 < solubility< 1000
Very slightly soluble	1000 < solubility < 10000
Practically in soluble	solubility>10000

Solid liquid Dispersions[7, 8,9,10] system concepts is given by spireas and spridon (1992). Liquisolid system refers to powdered forms of liquid medication Formulated by converting the active substance into a non-volatile liquid to from a mixture Selecting at least one solid carrier material and admixing these components to

produce a non-adherent, free-flowing and compressible liquid/powder mass admixture. To optimize flow and compressibility amount of drug and carrier ratio is constant. Liquisolid system is a novel concept of drug delivery via oral route. This technique is applied to water insoluble drugs and lipophilic drugs to sustain their release. Formulation and manufacture of the liquisolid tablets is quite simple method according to new mathematical model described by Spire's et al. It involves dissolving the drug in suitable non-volatile solvent and then adding this liquid medication to the mixture of carrier and coating materials. Mixing of this will lead to liquisolid system which is subjected to tabletting by direct compression. Increase in dissolution rate and in turn improvement in bioavailability is observed in case of poorly water-soluble drugs. However, sustained effect is achieved in case of water soluble drugs. By use of this technique, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powder with acceptable flow properties and compression behavior using suitable powder excipients. The liquisolid system shows acceptable flow properties and compressibility. Liquid lipophilic drugs or water insoluble solid drugs dissolved in nonvolatile solvent and this liquid medication can be converted into free flowing, non-adherent, dry looking and readily compressible powders with use of carrier and coating materials. As the drug is in the form of liquid medication it is either solublised or molecularly dispersed state. Due to increased wetting and surface area for dissolution. Liquisolid tablet of water insoluble drugs shows improved dissolution properties and in turn increase in bioavailability. Also, the low cost incurred during the manufacture ofliquisolid system proves them useful with respect to industrial production using this technique.

The term solid dispersion refers to a group of solid products consisting of at least two different components generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chiou and Riegelman defined solid dispersions as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states"[11]. Sekiguchi and Obi in 1961 first developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg et al. demonstrated that a certain fraction of the drug might also be molecularly. Dispersed in the matrix, forming solid solutions, while other investigators reported that the drug might be embedded in the matrix as amorphous materials[12].

MATERIALS AND METHODS:

Repaglinide was Supplied by Pharma Train, PEG 400 purchased from Colorcon Pvt Ltd, Avicel PH102(MCC) purchased from FMC Bio Polymer Pvt Ltd (Mumbai), Aerosil, Magnesium Stearate, Banana Powder purchased from SD Fine Chemicals (Mumbai).

Formulation of Repaglinide Immediate Release capsule by liquisolid compacts method:

Repaglinide drug was initially dispersed in the nonvolatile solvent systems PEG 400 termed as liquid vehicles with different drug: vehicle ratio. Then a mixture of carrier (Avicel pH 102) was added to the above liquid by continuous mixing for a period of 10 to 20 minutes in a mortar. Then to the above mixture coating material (aerosil) was added and mixed thoroughly. The amount of carrier and coating materials added were based on the 'R' value. To the above binary mixture disintegrant like banana powder and other remaining additives such as lubricant (Magnesium stearate) are added according to their application and mixed in a mortar. The final mixture was filled in to the capsule.

Table 2: Formulation of Repaglinide immediate release capsules

Formulation	Ingredients (mg)					
	Repaglinide	PEG 400	Carrier Material (MCC)	Coating Material (Aerosil)	Magnesium stearate	Banana powder
RIC1	100	50	200	15	5	10
RIC2	100	50	200	15	5	20
RIC3	100	50	200	15	5	30
RIC4	100	100	200	15	5	10
RIC5	100	100	200	15	5	20
RIC6	100	100	200	15	5	30
RIC7	100	150	200	15	5	10
RIC8	100	150	200	15	5	20
RIC9	100	150	200	15	5	30

EVALUATION OF TABLETS:

A) Pre-Compression studies:

1. Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured, and angle of repose was calculated using the following equation[11].

$$\theta = \tan^{-1} (h/r)$$

Where:

θ = angle of repose; h = height in cms; r= radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Table 3: Angle of Repose Limits-Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2. Density:

a. Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula[13]

Bulk density = weight of powder/ Bulk volume.

$$Db = M/V_0$$

Where, M = mass of the powder; V_0 = bulk volume of the powder.

b. Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder

Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula[13].

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f).$$

Where, M = mass of the powder; V_f = tapped volume of the powder.

3. Carr's Index: Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down[5]. The formula for Carr's index is as below:

$$\text{Compressibility index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

4. Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flow ability of a powder[5].

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table 4: Compressibility index limits

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

B) Post compression studies:

1. General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

2. Average weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage[14].

$$\text{\% weight variation} = \frac{\text{Highest weight of filled capsule in grams – average weight}}{\text{Average weight of filled capsule in grams}} \times 100$$

Table 5: Weight variation tolerance for uncoated tablets

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

3. Assay Procedure.

Weigh and finely powder not less than 20 capsules. Transfer an accurately weighed portion of the powder equivalent to about 10mg of model drug a 10 ml volumetric flask. Add approximately 5ml of methanol shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with water to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with water[15].

Calculate the quantity in mg of model drug in the portion taken by the formula

assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

4. *In vitro* Dissolution Study:

900 ml of 0.1 N HCL buffer was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37^0C±0.5^0C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 60 minutes at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions.

Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =243 nm using a UV-spectrophotometer (Lab India)[16,17].

Table 6: Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	3, 6, 9, 12, 15, 18, 21, 24, 27 and 30mins
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	243 nm

C) *In vitro* Release Kinetics Studies:[14]

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics:

It defines a linear relationship between the fractions of drug released versus time.

$Q=k_0t$.

Where, Q is the fraction of drug released at time t and $k_o$is the zero-order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$Log\ C = Log\ C_o - kt/2.303$

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of log % drug remaining vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

RESULTS AND DICUSSION

Evaluation Test parameters:

A) Pre-compression studies:

The prepared capsules were evaluated for their flow properties; the results for the blends of compression capsules were shown in Table. The bulk density and the tapped density for all formulations were found to be almost similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 respectively, indicating good flow and compressibility of the blends. The angle of repose for all the formulations was found to be 25.13-37.82 which indicating passable flow.

Table 7: Pre-compression studies of Repaglinide capsules

Formulation code	Bulk densitym(mg)	Tapped density (mg)	Cars index	Hausner's ratio	Angle of repose
RIC1	45	49	8.16	1.09	25.93
RIC2	48	55	12.73	1.15	32.48
RIC3	43	48	10.42	1.12	25.13
RIC4	53	57	7.02	1.08	25.28
RIC5	49	56	12.5	1.14	32.31
RIC6	45	51	11.76	1.13	31.34
RIC7	46	50	8.00	1.09	25.61
RIC8	43	48	10.42	1.12	26.74
RIC9	46	55	16.36	1.20	37.82

***n=3**

B) Post compression studies:

1. Drug Content (%) and Weight variation:

The variation in weight was within the range of ±5% complying with pharmacopoeia specifications of USP. The drug content was found to be within limits 98 to 102 %.

Table 8: Post compression studies of Repaglinide capsules

Batch	Drug Content (%)	Weight variation
RIC1	99.12	394
RIC2	100.73	407
RIC3	99.74	415
RIC4	98.98	448
RIC5	99.67	456
RIC6	99.83	462
RIC7	101.32	497
RIC8	100.87	505
RIC9	99.92	512

2. *In-vitro* Dissolution Studies:

Table 9: *In-vitro* Dissolution Studies of Repaglinide Immediate Release Capsules

TIME (min)	% DRUG RELEASE								
	RIC1	**RIC2**	**RIC3**	**RIC4**	**RIC5**	**RIC6**	**RIC7**	**RIC8**	**RIC9**
0	0	0	0	0	0	0	0	0	**0**
3	24	23	35	27	26	24	39	63	**65**
6	31	35	46	35	39	31	61	76	**86**
9	38	41	58	49	51	53	83	83	**95**
12	53	50	72	63	68	68	97	95	**100**
15	64	59	79	75	80	81	98	99	
18	71	70	85	86	89	95	98		
21	78	82	92	97	97	99			
24	82	89	99	99	100				
27	85	94							
30	91	97							

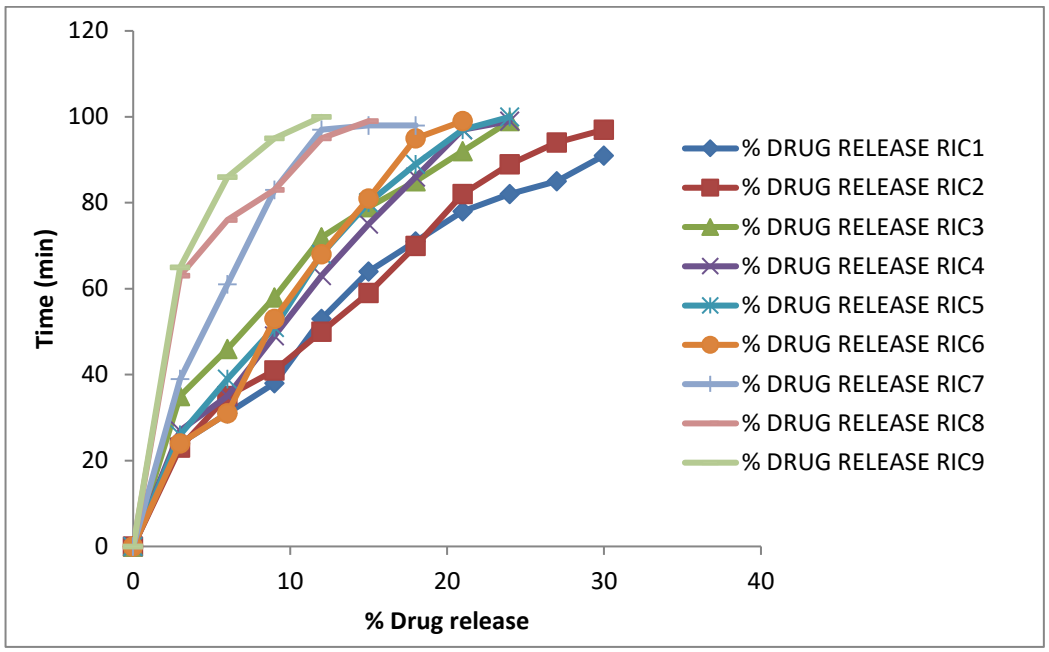

Fig 1: Dissolution profiles of Repaglinide Capsules for RIC1 to RIC9 formulations

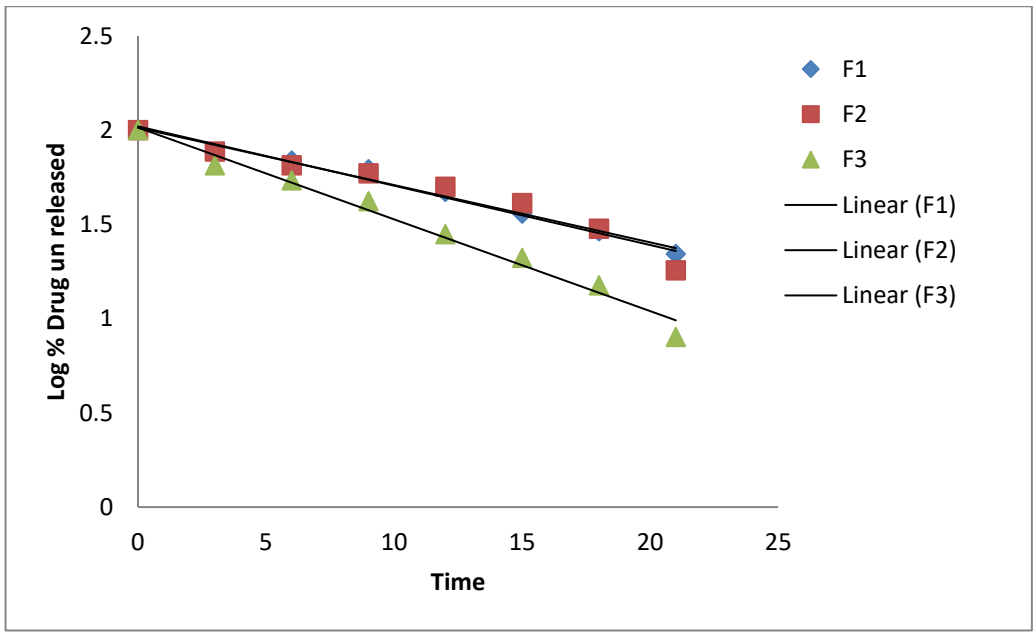

Figure 2: First order plot for RIC1, RIC2 and RICF3 formulations

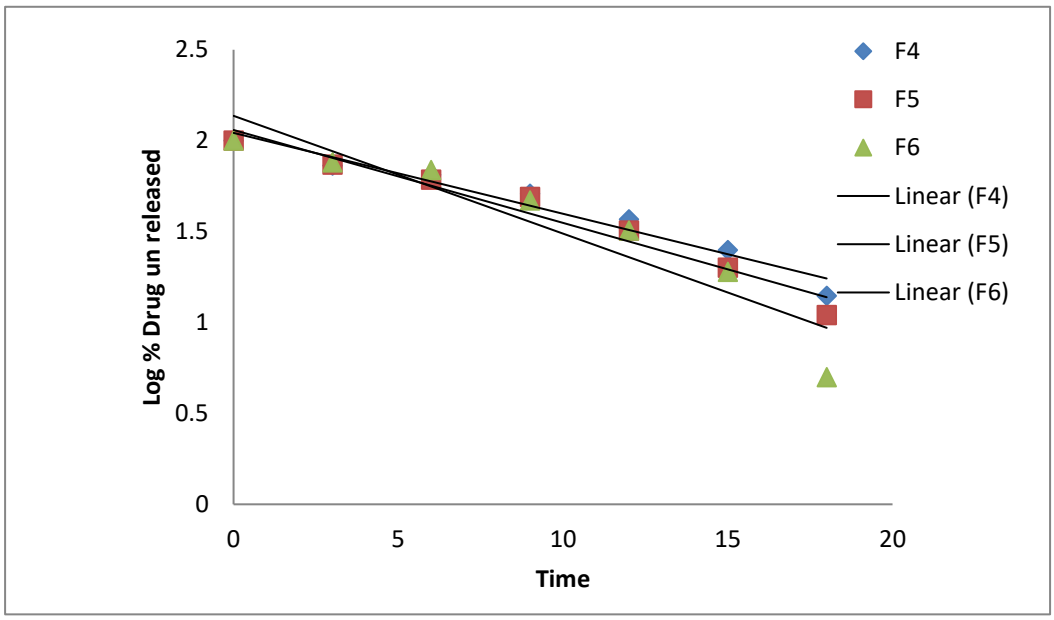

Figure 3: First order plot for RIC4, RIC5 and RIC6 formulations

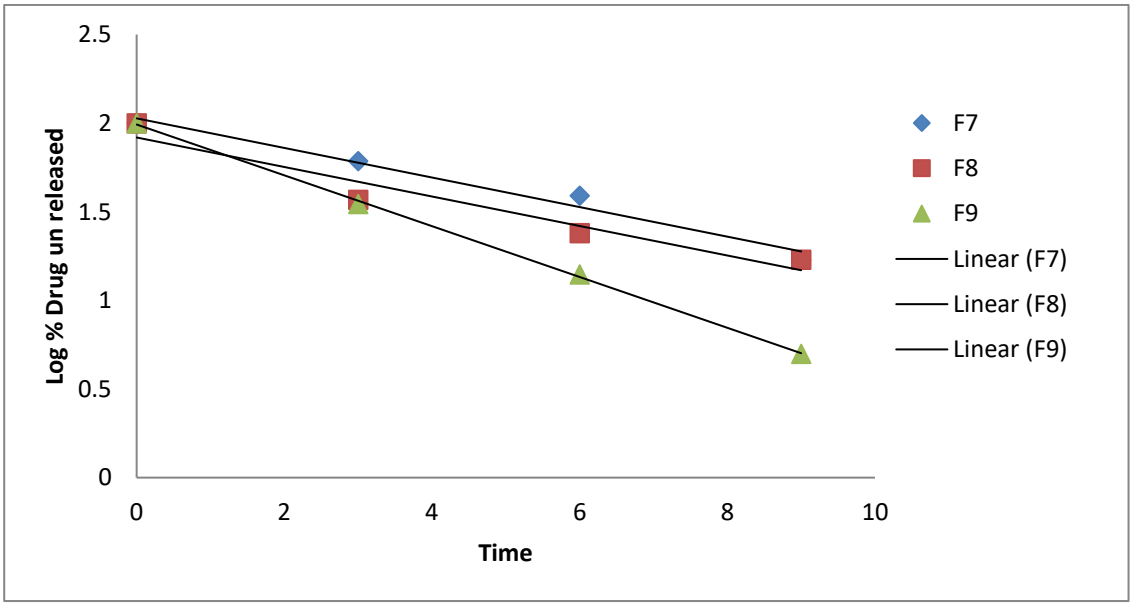

Figure 4: First order plot for RIC7, RIC8 and RIC9 formulations

Table 10: R^2 Values for best formulation F9

Formulation code	Zero order	First order
F9	0.789	0.999

SUMMARY AND CONCLUSION

Repaglinide tablets were formulated by using liquid solid compaction method using Poly ethylene glycol as liquid vehicle, Avicel pH 102 as carrier, aerosil as coating material, Banana powder as disintegrating agent and talc as glidant. Compatibility studies were carried out for the physical mixture and the drug was found to be compatible with all excipients used in different formulations. The blends were filled into capsules and were analyzed for the parameters such as average weight, % assay and in vitro dissolution. Concluded that Formulation RIC9 shows better release when compared with other formulations.

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