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Research Article

FORMULATION AND EVALUATION OF REPAGLINIDE FAST DISSOLVING TABLETS

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ABSTRACT

Repaglinide is a meglitinide derivatives used in the treatment of type 2 diabetes mellitus belongs to BCS Class II drug with short half-life(1 hr.), having poor oral bioavailability i.e. nearly < 60% and is a suitable candidate for solubility enhancement and fast dissolving tablets. Initially solubility forRepaglinide was enhanced by solid dispersion techniques like 1) drop melt method(D1) 2) solvent evaporation method(D2) 3) solvent deposition(D3) 4) combination of 2& 3techniques(D4). Then the bestRepaglinidedispersion(D4) was selected based on dissolution and formulated as tablet dosage form using various diluents and super disintegrants. The final formulation was selected based on dissolution profile that is formulation with MCC(micro crystalline cellulose) as a diluents and cross povidone as a super disintegrants. Accelerated stability studies for final formulation were conducted and reported for three months.

Keywords: Repaglinide, Fast dissolving Tablets, Solid dispersion Technique.

1. INTRODUCTION[1,2]

40-60 % of drugs used in pharmaceutical industry are poorly water soluble or lipophilic compounds. Poorly water soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the GIT. The dissolution characteristic of poorly water soluble drugs can be enhanced by several methods like pH adjustment, salt formation, co-crystallization, co-grinding, co-solvency, hydrotropy, solubilization, size reduction like micronization, nanotechnology, Complexation, and drug dispersion in carriers.

Repaglinide is a meglitinide analogue used in the treatment of type II Diabetes mellitus. It controls high blood sugar levels and helps in preventing kidney damage, blindness, nerve problems, loss of limbs, sexual problems & heart complications. This should not be used in type I Diabetes mellitus. It is a poorly water soluble drug belongs to BCS class II drug with short biological half-life(1 hr), because of these two reasons it is having poorly oral bioavailability(<60 %). Its solubility was enhanced by solid dispersion technique, which is a kind of drug dispersion in carriers method. In the solid dispersion technique drop melting, solvent evaporation, solvent deposition method and combination of solid dispersion and solvent deposition methods were used. In drop melting and solvent evaporation methods PEG 6000 was used as a carrierimparts hydrophilicity to the Repaglinide. In solvent deposition method MCC was used as carrier because of its amorphous nature it increases the surface areaof Repaglinide by that dissolutionafter deposition by solvent(Methylene chloride).

In this study, an attempt has been made to formulate fast dissolving tablets by using best

Repaglinide dispersion using super disintegrants like Sodium starch glycolate, Cross-carmellose sodium & Cross-povidone by selecting best directly compressible diluents- Starch & MCC. The fast dissolving tablets dissolve or disintegrate in the GIT and enhance bioavailability of poorly water soluble drug i.e. Repaglinide.

2. MATERIALS AND METHODS

Repaglinide & all the chemicals were gifted by SK Health care Pvt. Ltd., Bolaram, Hyderabad.

2.1 Preparation of Repaglinide standard calibration curve in pH 5 Acetate buffer

10mg of Repaglinide is accurately weighed and dissolved in 10ml methanol contained in a volumetric flask to result in stock solution of 1000 ug/ml, this solution is further diluted employing acetate buffer of pH5. The various concentrations of Repaglinide prepared are 10 ,20 ,30 , 40 ,50 ,60 ug/ml . The absorbance of various solutions of Repaglinide are determinedspectrophotometrically at 283nm employing UV –double beam spectrophotometer (model ELICO SL 169) using acetate buffer of pH 5. The concentrations of Repaglinide and corresponding absorbances are given in **Table.** The absorbances were plotted against concentration ofRepaglinide performing two trails shown in **Figure.**

2.2 Preparations of Repaglinide dispersions using solid dispersion techniques enhancement techniques[3,4]

2.2.1 Drop melting method

Ingredients

Repaglinide - 100mg
Polyethylene glycol - 200mg

Procedure

200mg of polyethylene glycol was taken in a china-dish melted at 70 ^{0}C. Now dispersed the 100 mg of Repaglinide in molten PEG by maintaining its temperature. The above mixture was mixed thoroughly and allowed to dry at 60 ^{0}C & passed the through sieve number 100.

2.2.2Solvent evaporation method

Ingredients

Repaglinide - 100mg
Polyethylene glycol (PEG) - 200mg
Methylene chloride - 10 ml

Procedure

10ml of Methylene chloride was taken in a RBF; PEG was added. Now, the drug was added to the above mixture. And solvent was withdrawn by using rotary suction pump and product was dried, scraped and passed through the sieve no.100.

2.2.3 Solvent deposition method

Ingredients

Repaglinide- 100mg
Methyl cellulose - 200mg
Methylene chloride - 10ml

Procedure

10ml of methylene chloride was taken in the RBF. Then the MCC was added, which doesn't dissolve in methylene chloride. Then the drug was added to the above mixture. And solvent was withdrawn by using rotary suction pump and product was dried, scraped and passed through the sieve no.100.

2.2.4 Combination of solid dispersion and solvent deposition method

Ingredients

Repaglinide - 100mg
Polyethylene glycol (PEG) - 200mg
Micro crystalline cellulose - 200mg
Methylene chloride - 10 ml

Procedure

10ml of methylene chloride was taken in the RBF. Then, added the PEG and MCC and then the drug was added to the above mixture. The solvent was withdrawn by using rotary suction pump. Mixture is then scraped, dried and passed it through the sieve number 100 to get the powdered form of the formulation.

2.3 Preparation of fast dissolution tablets using direct compression method for the selected Repaglinide dispersion (D4)[5]

2 mg equivalent Repaglinide dispersion was taken and passed through sieve no-60 and mixed with diluents, disintegrating agents, glidants& lubricants in a poly bag which were already passed from sieve no-40. The tablets were compressed by using 7.0 mm, round, standard flat punches, with an average tablet weight of 50 mg and hardness of 3-4 kg/cm2 on a 16 station Cadmach Tablet compression machine.

3. EVALUATION

3.1 Estimation of % drug content for the prepared Repaglinide dispersions[6]

10mg of each sample was weighed and diluted to 10mlwith methanol in a volumetric flask this gives 1000 µg/ml(stock1). This is further diluted to 10ml by taking 1ml with methanol gives 100µg/ml(stock2). FromStock2 take 1ml and diluted to 10ml with acetate

buffer pH 5.Absorbance of diluted solutions were taken by using UV-Spectrophotometer at 283nm wave length. These were reported in thefollowing table3 .

3.2 In-vitro dissolution studies of Repaglinide dispersions prepared by solid dispersion technique[7]

Dissolution rate studies were performed in 900ml of pH 5 acetate buffer at 37 ± 0.5 ^{0}C,using 8-station USP type-II (paddle) apparatus with paddle rotating at 75 rpm .Pure drug(2 mg) and dispersions prepared by solid dispersion technique each containing 2 mg equivalent of drug were subjected to dissolution. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically analyzed for the drug content at 283 nm. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t. percentage of drug released at each time interval was calculated from the formula.

% Drug dissolved = $(A_t/A_s)\times(D_s/D_t)$ × dilution factor.

Here, A_t – test absorbance

A_s – standard absorbance

D_s- standard dilution

D_t - test dilution.

3.3 Estimation of % drug content for the prepared Repaglinide fast dissolving tablets

10 tablets were taken in a mortar which are selected randomly andgrounded finely, from this on tablet equivalent amount of powder was weighed accurately. This was placed in 10 ml of methanol and sonicated for 5 minutes and diluted properly and drug content was analysed using UV-Spectrophotometer at 283nm wave length and reported in thetable 6.

3.4 In-vitro dissolution studies for fast dissolving Repaglinide tablets

Dissolution rate studies were performed in 900 ml of pH 5 acetate buffer at 37 ± 0.5 ^{0}C,using 8-station USP type-II (paddle) apparatus with paddle rotating at 75 rpm .2 mg equivalent of Repaglinide fast dissolution tablet was placed in dissolution basket. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically analyzed for the drug content at 283 nm. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t. percentage of drug released at each time interval was calculated from the formulation.

% Drug dissolved = $(A_t/A_s)\times(D_s/D_t)$ × dilution factor.

Here, A_t – test absorbance

A_s – standard absorbance

D_s- standard dilution

D_t - test dilution.

3.5 Stability studies for final formulation[8-10]

Accelerated stability studies were carried out for 3 months at 40 ^{0}C/75% RHby observing physicalparameters, assay and dissolution for final formulation by comparing for further three months.

Table 1: Formula for fast dissolving tablets per unit

Name of the ingredient	T1	T2	T3	T4	T5
Repaglinide equivalent to 2 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Microcrystalline cellulose		39 mg	35 mg	35 mg	35 mg
Starch	39 mg				
Sodium starch glycolate			4 mg		
Cross-carmellose sodium				4 mg	
Cross povidone					4 mg
Mg. Stearate	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Talc	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Total weight of the tablet	50 mg	50 mg	50 mg	50 mg	50 mg

Table 2: Repaglinide standard calibration curve in pH 5 Acetate buffer at 283 nm

Time	Pure drug	D1	D2	D3	D4
0	0	0	0	0	0
5	10.14	32.6	28.98	36.95	45.65
10	18.11	47.82	37.68	46.37	58.7
20	25.36	59.42	45.65	57.97	68.11
30	39.85	71.01	51.45	66.66	78.98
45	47.1	66.66	57.97	73.91	85.5
60	39.13	61.59	64.5	73.18	91.3

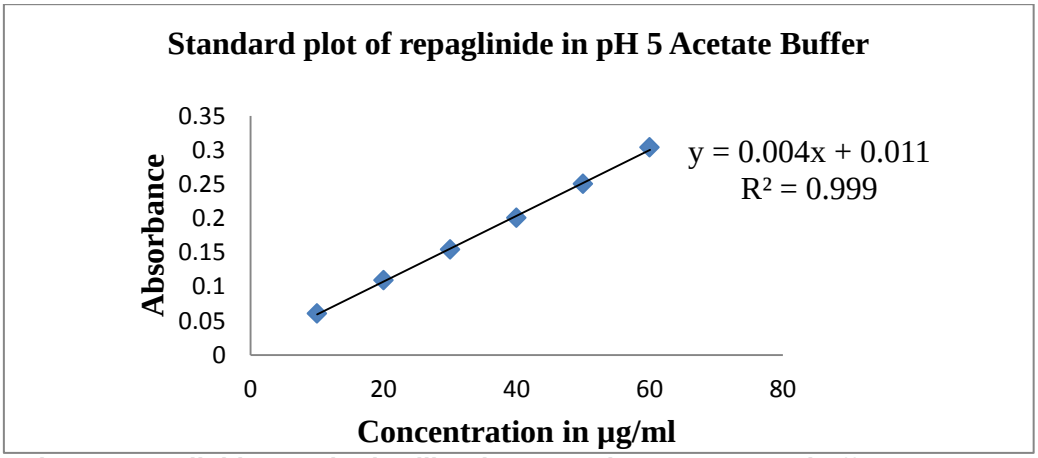

Fig. 1: Repaglinide standard calibration curve in pH 5 Acetate buffer at 283 nm

Table 3: % drug content for Repaglinide dispersion

Formulation code	% Drug content
Pure drug	95.56
D1	98.54
D2	97.25
D3	99.25
D4	99.42

Table 4: Dissolution data of Repaglinide dispersion in pH 5 Acetate buffer(283 nm)

Concentration (ug/ml)	Absorbance		
	Trail 1	Trail 2	Average
10	0.0602	0.0640	0.0621
20	0.1092	0.1041	0.1066
30	0.1513	0.1425	0.1469
40	0.2076	0.2096	0.2086
50	0.2733	0.2763	0.2748
60	0.367	0.3833	0.3751

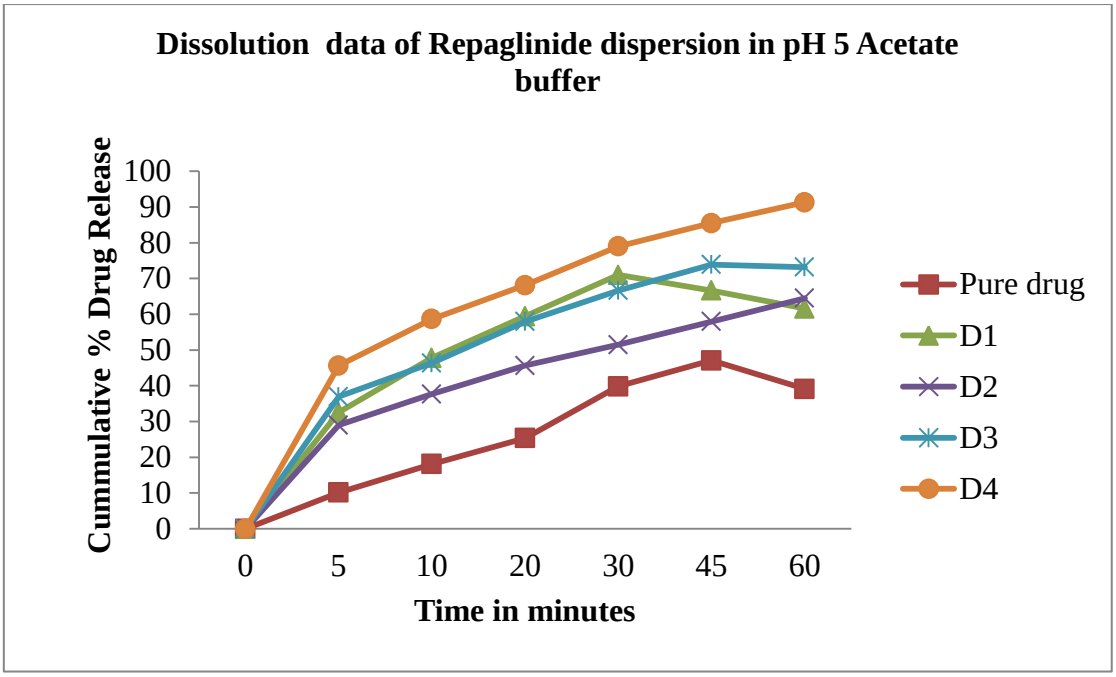

Fig. 2: Dissolution data of Repaglinide dispersions in pH 5 Acetate buffer (283 nm)

Table 5: DE_{30}data of Repaglinide dispersions

Sample	DE_{30}(%)
Pure drug	21
D_1	48
D_2	36
D_3	46
D_4	55

Table 6: % drug content of Repaglinide fast dissolving tablets

Formulation code	% Drug content
T1	99.05
T2	99.38
T3	99.26
T4	98.96
T5	99.18

Table 7: Dissolution data for Repaglinide fast dissolution tablets

Time	T1	T2	T3	T4	T5
0	0	0	0	0	0
5	33.26	36.50	42.63	44.82	45.58
10	39.32	47.19	50.29	57.05	58.32
20	50.83	61.32	61.78	66.98	67.90
30	59.88	70.92	72.77	77.19	78.57
45	67.05	76.57	81.46	84.76	84.93
60	79.61	85.01	89.01	89.92	90.22

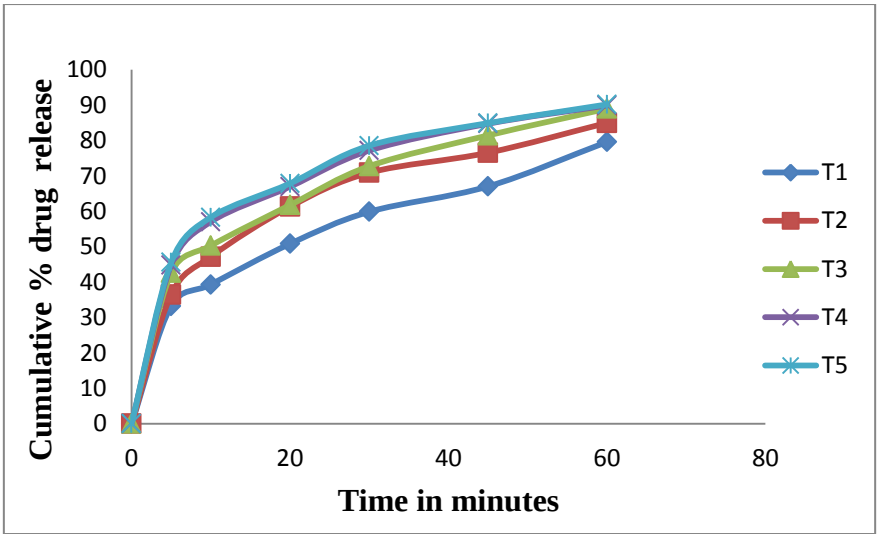

Fig. 3: Dissolution data for Repaglinide fast dissolving tablets in pH 5 Acetate buffer

Table 8:DE_{30}data for Repaglinide fast dissolving tablets

Formulation code	DE_{30}(%)
T1	40
T2	48
T3	49
T4	54
T5	**55**

Table 9: Stability data for final formulation(T_5) for three months

S.No.	Parameters	0 month	I month	II month	III month
1	Color	White	No change	No change	No change
2	Assay(%)	98.98	99.04	99.01	99.16
3	Dissolution	Shown bellow	Shown bellow	Shown bellow	Shown bellow

Table 10: Dissolution data for stability studies

Time in minutes	0 month	I month	II month	III month
0	0	0	0	0
5	45.58	44.89	46.61	44.92
10	58.32	59.02	58.56	60.70
20	67.90	66.81	68.06	67.35
30	78.57	77.98	78.02	79.62
45	84.93	84.53	83.84	86.03
60	90.22	89.86	90.72	91.26

4. RESULTS AND DISCUSSION

The present analytical methods obeyed Beer-Lambert's law in the concentration range 10-60 µg/ml. The values of correlation coefficient for the linear regression equation were found to be more than 0.997 for acetate buffer of p^H 5 indicating a good positive correlation between concentration of Repaglinide and the corresponding absorbance values. The linear regression equations for Repaglinide calibration curves are Y= (0.005) x+0.000(shown in fig 1). Thus the method was

found to be suitable for the estimation of Repaglinide in the various products and in drug release studies. The % drug content for Repaglinide dispersions was between 95-100 %(shown in table 2).

From the dissolution data, it was observed the solubility or dissolution enhancement followed in the order(shown in table 4) for Repaglinide dispersions.

$D_4 > D_3 > D_2 > D_1 >$ Pure drug

D4 was showing high dissolution profile as well as $DE_{30\%}$ compared to other dispersions(shown in table 4 & 5). Hence, it was selected for preparing fast dissolution tablets(shown in table 1) and % drug content observed between 98-99 %(shown in table 6). The fast dissolving tablets prepared by using MCC was shown better dissolution profile compared to starch as diluent(shown in table 7 & figure 2). The fast dissolving tablets prepared using different super disintegrants shown following order to enhance the dissolution of Repaglinide (shown in table 7)

$T_5 > T_4 > T_3$

From the dissolution data, it was observed that T_5 was shown better dissolution and $DE_{30\%}$(shown in table 8), hence it was selected as final formulation and conducted accelerated stability studies for three months. From these studies, it was found that there is no change of physical, chemical parameters and dissolution profile for three months(shown in table 9 & 10).

5. CONCLUSION

The final formulation was selected based on the in-vitro dissolution profile as well as dissolution efficiency ($DE_{30\%}$) of the formulation. The final formulation was also stable, which was concluded from accelerated stability studies conducted for 3 months.

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