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Formulation and evaluation of anti-diabetic activity of repaglinide nanosuspension

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ABSTRACT

Diabetes is one of those metabolic disorders that are typically characterized by an increase in blood glucose level, glycosuria and ketonemia. This widely spread disease and its complications result in thickening of vascular tissue, PVD, neuropathy and retinopathy. Repaglinide is the first member of the newer class of drugs that are designed to lower the postprandial glucose. The most prevalent problem faced by those drugs are very low solubility and thereby causing the oral delivery very inefficient leading to low bioavailability and improper dose and release proportionality. Research attempts are being put towards enhancing the oral bioavailability of repaglinide kind of lipophilic drugs to improve the clinical effect. Out of those methods to improve the solubility and bioavailability, Nano suspensions have been a promising method to facilitate the above problem. Nano suspensions can be applied to enhance the solubility of Repaglinide too. So, in this research, Repaglinide particle size reduction has been performed, and nanosuspensions were tested for their clinical efficacy invivo. A nanoprecipitation method was developed to prepare Repaglinide nanosuspension using poloxamer as a stabilizer. The prepared formulations had been tested for the clinical efficacy invivo in albino Wistar rats. The results showed that the nanosuspensions have been very efficient in lowering the postprandial blood glucose levels and also facilitated the consistent release of the drug, which is evident from the constant lowering of glucose level. The prepared nanosuspensions showed a very potent and found to clinically efficient compared to the pure drug and drug suspensions.

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INTRODUCTION

Diabetes is one of those metabolic disorders that is typically characterized by an increase in blood glucose level, glycosuria and ketonemia. This widely spread disease and its complications result in thickening of vascular tissue, PVD, neuropathy and retinopathy [1] . The blood sugar-lowering drugs are beneficial when used orally significant drawback of insulin being it is given in the form of injection. So recently there are three new classes of drugs that had been synthesized like alpha-glucosidase inhibitors, meglitinide analogues and thiazolidine-

diones. Out of those drugs, Repaglinide is the first member of the unique type of drugs that are designed to lower the postprandial glucose [2].

The most prevalent problem faced by those drugs are very low solubility and thereby causing the oral delivery very inefficient leading to low bioavailability and improper dose and release proportionality. Research attempts are being put towards enhancing the oral bioavailability of repaglinide kind of lipophilic drugs to improve the clinical effect. Out of those methods to improve the solubility and bioavailability, Nano suspensions have been a promising method to facilitate the above problem [3]. These are dispersion systems of colloids of nano-sized drug molecules which are dispersed in an aqueous medium with the surfactants. They are also defined as the biphasic systems that contain drug particles with a diameter of less than 1 micrometre. So it can be advocated that the nanosuspensions can be adopted to improve the water solubility of drugs both in aqueous and lipid solubility [4].

Repaglinide has a very poor water solubility, thus limiting its clinical efficacy and BA. As we know, the particle size reduction can dramatically enhance the solubility and bioavailability [5]. Nano suspensions can be applied to enhance the solubility of Repaglinide too. So, in this research, Repaglinide particle size reduction has been performed, and nanosuspensions were tested for their clinical efficacy invivo [6].

MATERIALS AND METHODS

Materials

All the chemicals used in the experiments were procured from SD Fine Chem LTD., Mumbai, India. Amazing Pharmaceuticals gift Cipla labs gifted drug Repaglinide, Mumbai and the polymer poloxamer.

EXPERIMENTAL ANIMALS

Adult Albino Wistar rats, both male and female, were used in evaluating the activity. They were kept in PP cages at a temperature around 25°C & 12-12hr dark/light cycles were maintained. They were fed with a standard pellet diet bought from Hindusthan Ltd., Bengaluru, and water ad libitum [7, 8].

Formulation of nanosuspensions

Nanosuspension was prepared by using the solvent evaporation method. Repaglinide was solubilized in 6ml of methanol at normal room temperature [9] [10]. The solution was poured into 20 ml aqueous solution containing different amounts of Lutrol F-68 maintained at a temperature of 30–40°C and stirred for 1 hr to allow the methanol to evaporate (Remi, High-speed stirrer, India.). Non-polar solvents were left to evaporate under a slow magnetic stirring of the nanosuspension, at room temp for 2 hours (Table 1) [11, 12].

Table 1: Formulation of repaglinide nanosuspension

Ingredients	F4	F7
Repaglinide (mg)	8	8
Methanol (ml)	6	_
poloxamer (%w/v)	0.25	_
Tween 80 (ml)	2	–
Aqueous solvent (ml)	20	20

EXPERIMENTAL DETAILS

The lab acclimatized albino Wistar rats were fasted for 24hrs with water ad libitum & injected intraperitoneally a dose of 120mg/kg of Alloxan monohydrate suspended in normal saline. After 1hr, the rats were provided feed ad libitum. The sugar levels were checked before administration of Alloxan and 24hr after administration of Alloxan with a glucometer. Rats were determined as diabetic when the blood sugar level was raised beyond 150mg/100ml of blood [13].

Grouping of animals

Group I - Normal control without the treatment of Alloxan.

Group II – Diabetic Control rats administered only vehicle (2ml/kg p.o) 2% v/v Tween 80.

Group III - Rats were administered with pure Repaglinide (0.1mg/kg/day p.o) suspended in 2% v/v Tween 80.

Group IV – Rats were administered with Repaglinide suspension (formulation F7) dose equivalent to 0.1 mg/kg p.o.

Group V – Rats were administered with Repaglinide nanosuspension (Formulation F4) dose equivalent to 0.1 mg/kg p.o.

The blood glucose levels of all the rats were noted in time intervals of 15min, 30min, 60min, 90min, 120min and 180min. Sequential differences and significance were calculated using one-way ANOVA, followed by Dunnet's T-test.

RESULTS AND DISCUSSION

The blood glucose levels of all the rats were noted to investigate the antidiabetic activity.

Table 2: Blood glucose levels of rats in all groups

Time in (min)	Blood sugar level (mg/dL) Mean ± S.E.M (n=6)				
	Normal control	Diabetic control	Repaglinide Pure drug	Repaglinide suspension	Repaglinide nanosuspension
15	93.667±0.76*	171.667±2.69	148.500±2.04*	139.667±1.52*	116.500±1.33*
30	95.167±1.22*	172.000±2.39	135.833±1.42*	113.883±2.88*	98.667±0.61*
60	94.500±0.85*	171.667±1.69	106.167±1.07*	94.167±1.07*	87.500±2.66*
90	94.167±0.82*	170.667±1.52	97.000±2.00*	82.500±0.76*	78.500±1.56*
120	94.833±1.58*	170.634±1.76	96.333±2.17*	81.167±1.44*	82.333±0.88*
180	95.333±1.16*	171.273±2.85	91.333±0.49*	98.167±2.77*	101.833±1.44*

*P>0.001,siginificant compared to control group

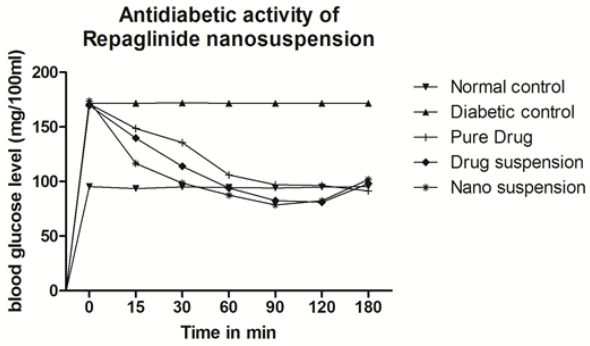

Figure 1: Antidiabetic activity of Repaglinidenanosuspension

The results were tabulated in Table 2 and lowering of blood glucose levels was compared in Figure 1.

Analyzing the results, the normal control ratsshowed a blood glucose level of 93-95 mg/dL of blood. Two days after the administration of Alloxan, the blood glucose level increased to 169-171 mg/dL of blood. Initially, the blood glucose level of all rats remained the same but soon after the administration of Repaglinide drug, the blood glucose level reduced to 148 mg/dL after15 min. The repaglinide suspension and nanosuspension have reduced the blood glucose level to 139 and 116 respectively, indicating that the drug suspension form had dissolved and released within 15 min and that in the nanosuspension was still more soluble. After 30 min, the blood glucose levels reduced to 135, 113 and 98 mg/dL. This level lowered to a minimum of 81 and 78 mg/dL with suspension and nanosuspension respectively at time 120 and 90 min suggesting that the drug nanosuspension form dissolved and absorbed into the gastric fluid just in 90 min. In contrast, it was a bit higher in case of drug suspension form proving the effect of surfactant and polymer in size reduction and finally, the relationship between the particle size reduction and solubility and activity [14].

Supporting the same the pure drug release was slow, and activity was lower compared to nanosuspension. The antidiabetic activity terminated after 120 min leading to an increase in blood glucose with both drug suspension and nanosuspension. But in contrast, the pure drug showed its maximum activity at a time after 120 min. It lowered the blood glucose level to 91mg/dL, which is better than the nanosuspension at that point If time. clears an assumption that the drug nanosuspension got absorbed into the blood as its solubility is enhanced and the pure drug which is less soluble showed its activity after a long time after administration [15].

From the above data, we can confirm that the drug nanosuspension form had a better activity combined with a faster onset of action, which is the most important necessity to treat diabetes postprandially. Correlating the principle of solubility enhancement through nanosuspension, we can say that the Repaglinide drug particle size was considerably lowered to improve the solubility.

CONCLUSION

Repaglinide nanosuspension was prepared using poloxamer as a stabilizer by nanoprecipitation technique. The prepared formulations had been tested for the clinical efficacy invivo in albino Wistar rats. The results showed that the nanosuspensions have been very efficient in lowering the postprandial blood glucose levels and also facilitated the consistent release of the drug, which is evident from the constant lowering of glucose level. The prepared nanosuspensions showed a very potent and found to clinically efficient compared to the pure drug and drug suspensions.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

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REFERENCES

[1] Zawar LR, Bari SB; 2018. Available from: https://doi.org/10.2174/1872211312666180713105959.

[2] Furman BL; 2007. Available from: https://doi.org/10.1016/B978-008055232-3.62525-5.

[3] Niemi M, Backman J, Kajosaari L, Leathart J, Neuvonen M, Daly A, et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. Clinical Pharmacology & Therapeutics. 2005;77(6):468–478. Available from: 10.1016/j.clpt.2005.01.018.

[4] Plosker GL, Figgitt DP; 2004. Available from: https://doi.org/10.2165/00019053-200422060-00005.

[5] El-Houssieny BM, Wahman LF, Arafa NMS. Bioavailability and biological activity of liquisolid compact formula of Repaglinide and its effect on glucose tolerance in rabbits. BioScience Trends. 2010;4(1):17–24.

[6] Tatiparthi R, Duraiswamy D, Bannoth CK. Method development and validation of metformin and Repaglinide in rabbit plasma by RP-HPLC. Fabad Journal of Pharmaceutical Sciences. 2010;35(2):69–75.

[7] Sastre AA, Vernooij RW, Harmand MGC, Martínez G. Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database of Systematic Reviews. 2017;Available from: 10.1002/14651858.cd003804.pub2.

[8] Nattrass M; 2000. Available from: https://doi.org/10.12968/hosp.2000.61.2.1275.

[9] Berecka A, Gumieniczek A, Hopkaa H. Development and Validation of a New High-Performance Liquid Chromatography Method for the Determination of Gliclazide and Repaglinide in Pharmaceutical Formulations. Journal of AOAC INTERNATIONAL. 2006;89(2):319–325. Available from: 10.1093/jaoac/89.2.319.

[10] Okunlola A, Adebayo AS, Adeyeye MC. Development of repaglinide microspheres using novel acetylated starches of bitter and Chinese yams as polymers. International Journal of Biological Macromolecules. 2017;94:544–553. Available from: 10.1016/j.ijbiomac.2016.10.032.

[11] Tatiparthi R, Duraiswamy D, Bannoth CK. Method development and validation of metformin and Repaglinide in rabbit plasma by RP-HPLC. Fabad Journal of Pharmaceutical Sciences. 2010;.

[12] Ebrahimi HA, Javadzadeh Y, Hamidi M, Jalali MB. Repaglinide-loaded solid lipid nanoparticles: effect of using different surfactants/stabilizers on physicochemical properties of nanoparticles. DARU Journal of Pharmaceutical Sciences. 2015;23(1). Available from: 10.1186/s40199-015-0128-3.

[13] Ahrén B, Pacini G; 2005. Available from: https://doi.org/10.1111/j.1463-1326.2004.00361.x.

[14] Varshosaz J, Minayian M, Ahmadi M, Ghassami E. Enhancement of solubility and antidiabetic effects of Repaglinide using spray drying technique in STZ-induced diabetic rats. Pharmaceutical Development and Technology. 2017;22(6):754–763. Available from: 10.3109/10837450.2016.1143001.

[15] Md, Sarfaraz, Lingareddy B, Doddayya H, Rajagopal HU. Design and in-vitro evaluation of gastro retentive floating tablets of Repaglinide. International Journal of Drug Development and Research. 2013;.

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