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FORMULATION AND EVALUATION OF PIOGLITAZONE NANOEMULSION

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ABSTRACT

The aim of the present study was to develop nanoemulsion formulation of pioglitazone to enhance the water solubility as well as bioavailability of drug. Three formulations of O/W nanoemulsions were prepared by the high pressure homogenization method by using different oil and co solvents. Pseudo ternary phase diagrams were designed to pick up the actual desired concentration of oil and co solvents used to obtain the nanoemulsion region. The study recommended that nanoemulsion significantly enhanced the solubility of pioglitazone so that it simultaneously enhances the bioavailability of pioglitazone.

Key Words:- Pioglitazone, Nanoemulsion, High pressure homogenization.

INTRODUCTION

Nanoemulsions are part of a broad class of multiphase colloidal dispersions. Although some lyotropic liquid crystalline phases, also known as 'micellar phases', 'mesophases', and 'microemulsions', may appear to be similar to nanoemulsions in composition and nanoscale structure, such phases are actually quite different. By contrast, nanoemulsions do not form spontaneously; an external shear must be applied to rupture larger droplets into smaller ones. Compared to microemulsion phases, relatively little is known about creating and controlling nanoemulsions (Mason *et al*., 2006).

Nanoemulsion is a heterogeneous system and it consist of two immiscible phase, one phase is oil phase other is aqueous phase, while the droplet is of submicron size range of 5-200nm. It is thermodynamically stable, optically clear and transparent.

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Now-a-day's nanoemulsions are frequently used for various purpose like delivery of vaccine, DNA encoded drug, antibiotics, cosmetic and topical preparations and can be administrated via various routes like oral, pulmonary, ocular and transdermal etc (Nishi Thakur *et al*., 2012).

Pioglitazone was an Antidiabetic drug. Pioglitazone is used for the treatment of diabetes mellitus type 2 either alone or in combination with a sulfonylurea, metformin, or insulin. There was, however, no statistically significant difference in the main composite outcome studied: death, cardiovascular events and revascularizations, and a higher risk of heart failure in the Proactive trial. There is no conclusive evidence of macrovascular benefit with pioglitazone or any other antidiabetic medication, but metformin. There was no evidence of increased all-cause mortality or cardiovascular mortality found with pioglitazone; some studies suggest reduced risk of all-cause and cardiovascular mortality with pioglitazone (low strength of evidence) (Isley William, 2006).

MATERIALS AND METHODS

Pioglitazone was acquired as a gift sample from Sashun Pvt. Ltd. Instrument used for the formulation and evaluation of Nanoemulsion like UV spectrophotometer, FTIR, High pressure homogenizer. And all solvents used in the formulation are selected as analytical grade solvents.

Method of Preparation of Nanoemulsion

High-Pressure Homogenization

This technique makes use of high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1nm). In a high-pressure homogenizer, the dispersion of two liquids (oily phase and aqueous phase) is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion. Homogenizers of varying design are available for lab scale and industrial scale production of nanoemulsions. This technique has great efficiency, the only disadvantage being high energy consumption and increase in temperature of emulsion during processing (Chouksey *et al*., 2011).

Evaluation of Nanoemulsion:

Droplet size and size distribution

Droplet size was determined by photon correlation spectroscopy (PCS) that analyzes the fluctuations in light scattering due to Brownian motion of the droplets using a Zetasizer (1000 HS, Malvern Instruments). The formulation (0.1 ml) was dispersed in 50 ml of water in a volumetric flask, mixed thoroughly with vigorous shaking and light scattering was monitored at 25 °C a 90 ° angle (Shafiq S *et al*., 2007).

Solubility determination

Excess amount of Pioglitazone was added to 1 ml of the nanoemulsion NEB1 and was shaken at 37±0.5℃ in a water bath shaker for 72 h. After 72 h nanoemulsion was centrifuged at 3000 rpm for 15 min. The supernatant was filtered using 0.45 µm filter membrane. An aliquot amount was diluted with methanol and analyzed by U.V spectrophotometer (Fernandeza P *et al*., 2004).

Mean Particle Size and Particle Size Distribution

The mean particle size and particle size distribution affects saturation solubility, dissolution rate, physical stability, and *in vivo* performance of nanoemulsions. The particle size distribution and its range named polydispersity index (PDI) can be determined by laser diffraction (LD), photon correlation spectroscopy, microscope, and coulter counter. PDI gives the physical stability of nanoemulsions and should be as lower as possible for the long-time stability of nanoemulsions. A PI value of 0.1 to 0.25 shows a fairly narrow size distribution and PI value more than 0.5 indicates a very broad distribution. LD can detect and quantify the drug microparticles during the production process. It also gives a volume size distribution and can be used to measure particles ranging from 0.05 up to 2000 µm. The coulter counter gives the absolute number of particles per volume for the different size classes. It is more efficient and suitable than LD to quantify the contamination of nanoemulsions (Chen Y *et al*., 2005).

Surface Charge (Zeta Potential)

Surface charge properties of the nanoemulsions are studied through zeta potential. The value of particle surface charge indicates the stability of nanoemulsions at the macroscopic level. A minimum zeta potential of ±20 mV to ±30 mV is required for electro statically stabilized. The zeta potential values are commonly calculated by determining the particle's electrophoretic mobility and then converting the electrophoretic mobility to the zeta potential. Electro acoustic technique is also used for the determination of the zeta potential in the areas of material sciences (Peter *et al*., 1996).

Invitro drug release studies:

The Static Franz diffusion cell was used for studying the *in vitro* release of the nanoemulsion. A cellulose acetate membrane was adapted to the terminal portion of the cylindrical donor compartment. A 10 mL portion of the nanoemulsion containing drug, sufficient for establishing sink conditions for the assay was placed into the donor compartment. The receptor compartment contained 90 mL of 0.2M Phosphate buffer solution of pH 7.4 maintained at 37°C under mild agitation using a magnetic stirrer. At specific time intervals, aliquots of 1mL were withdrawn and immediately restored with the same volume of fresh phosphate buffer. The amount of drug released was assessed by measuring the absorbance at 268 nm using a single beam UV spectrophotometer (Shah P *et al*., 2010).

RESULT AND DISCUSSION

The results for all the three formulations were shown in table no: 2 & 3. From the datas the results can be concluded as follows: When comparing the solubility profile of all the formulation with pure drug with the help of different oils and surfactant, it concluded that P3 formulation shows good solubility pattern when compared

other two formulations. It may be due to the concentration homogenization effect. Among all the three formulation P3 shows very less particle size in nano range of about 104.6nm and also shows good dispersibity (PDI) and surface charge potential when compared to other two formulation, due to the optimized concentration of the of both hydrophilic and lipophilic surfactant and tween 80 and span 80 surfactant. The *invitro* drug release studies shows that P3 formulation shows maximum release of drug at 5 minutes time interval itself i.e., 92.54% of drug release at 10 minutes itself, when compared to all the other formulation.

Table 1. Composition of Pioglitazone Nanoemulsion

Formulation	Pioglitazone	Oil – Miglyol	Oil – Myritol	Oil –Myritol+ Miglyol	Surfactant -Span 80	Tween 80	Pressure by homogenizer
P1	20 mg	50 mg	-	-	0.06%	0.25%	1000 psi
P2	20 mg	-	50mg	-	0.06%	0.5 %	2000 psi
P3	20 mg	-	-	25mg +25 mg	0.06%	0.75 %	3000 psi

Table 2. Solubility studies

Oil & Surfactant	Solubility (mg/ml)			
	Pioglitazone	P1	P2	P3
Miglyol + 0.06% Span 80 +0.25 % Tween 80	22.34	33.48	-	-
Myritol + 0.06% Span 80 +0.5 % Tween 80	18.92	-	45.88	-
Miglyol + Myritol + 0.06% Span 80 +0.75 % Tween 80	27.56	-	-	94.12

Table 3. Evaluation of Nanoemulsions P1-P3

Formulation code	P1	P2	P3
Particle size (nm)	224.8 nm	189.2 nm	104.6 nm
Zeta Potential (mV)	- 13.22	- 26.38	- 31.42
Poly Dispersibility Index (PDI)	0.304	0.429	0.290
Drug content in (%)	90.80	92.60	90.54

CONCLUSION

By Comparing the nano-emulsion size distributions and solvent physical properties (zeta potential, PDI and drug content) it shows that high pressure homogenization technique was an optimized technique for the formulation of Nanoemulsion. And also it shows that formulation containing both Miglyol and Myritol with 0.06% lipophilic surfactant and 0.75 % hydrophilic surfactant was a better choice for the formulation of nanoemulsion.

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