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Solubility Enhancement of Antihyperlipidemic Drug by Solvent Diffusion Technique

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Abstract

Poor aqueous solubility of drugs is major limiting factor with many new drugs in their successful launch in market in spite of their potential pharmacokinetic activity. Therefore, poor solubility is critical factor if the molecule is to survive the pharmaceutical development process. In the current work, it was planned to enhance the solubility of antihyperlipidemic drug by solvent diffusion technique. For this the drug clofibrate and excipients were procured and spherical agglomerates were prepared and evaluated. The findings of the study states the novelty the hypothesis.
Keywords: Solubility, Diffusion, Agglomerates

Introduction

Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Poor aqueous solubility of drugs is major limiting factor with many new drugs in their successful launch in market in spite of their potential pharmacokinetic activity. About 90% of all compounds in today's pharmaceutical drug delivery pipelines are reported to be poorly soluble in water. This process enormous problem for the industry for an active pharmaceutical ingredient cannot reach its molecular target in the body if the drug remains undissolved in the gastrointestinal tract (GIT) and is eventually excreted. Therefore, poor solubility is critical factor if the molecule is to survive the pharmaceutical development process. Even those molecules that would have highly beneficial effect on their physiological target would not be further developed if their bioavailability is limited by their solubility in water. Further poorly water-soluble drugs are generally administered at much higher dose than the actual dose in order to achieve necessary drug plasma level leading to improved adverse reaction and cost of therapy and often yields erratic pharmacological response and hence poor patient complains. In addition, the manufacturing cost would increase since a large amount of active pharmaceutical ingredient (API) might be consumed to develop and manufacture the drug product. [1]

Hyperlipidemia is a condition characterized by an elevation of any or all lipid profile and/or lipoproteins in the blood. Although elevated low density lipoprotein cholesterol (LDL) is thought to be the best indicator of atherosclerosis risk,

dyslipidemia can also describe elevated total cholesterol (TC) or triglycerides (TG), or low levels of high-density lipoprotein cholesterol (HDL). Hyperlipidemia is the major precursor of lipid related ailment such as atherosclerosis, coronary artery disease and also involved in sudden death syndrome. The main cause of hyperlipidemia includes changes in lifestyle habits in which risk factor is mainly poor diet. Although these techniques have commonly been used to increase dissolution rate of the drug, there are practical limitations with these techniques, the desired bioavailability enhancement may not always be achieved. [2] In the current work, it was concentrated on improvement of the solubility of clofibrate drug by solvent diffusion technique.

Experimental work

Identification and collection of all proposed drug material

The drug clofibrate and other required excipients were collected from Rouzel Pharma, Chandigarh as gift sample. All the collected material was used in the for the proposed work.

Preparation of clofibrate spherical agglomerates using solvent diffusion technique

Three dissimilar organic solvents as good solvent including methyl acetate (MA), ethyl acetate (EA) and isopropyl acetate (IPA) were employed as a dispersed phase for making oil-in-water emulsions (O/W). Crystallization was carried out in a cylindrical vessel equipped with three baffles. Clofibrate was dissolved in 15 ml of good solvent. The solvent solutions were then poured dropwise during 3 min, under stirring (500 rpm), into 485 ml of water containing 0.1% w/v emulsifier. Tween 80, SLS, PVP or HPMC were used as emulsifiers. After 15 min agitation by a propeller type stirrer, the agglomerates were separated from the solution by filtration under vacuum and then were placed in a thin layer in an oven at 60°C for 3 h. The solubility of organic solvents in water was the basis of the selection of the solvents in making solvent-in-water emulsion. [3]

Table 1 Formula for Clofibrate spherical agglomerates

Formulation Code	Clofibrate (mg)	SLS (%)	PVP (%)	Tween 80 (%)	HPMC (%)	Methyl acetate (ml)	Ethyl acetate (ml)	Isopropyl acetate (ml)
CLF F1	500	0.0130	00	00	00	20	60	20
CLF F2	500	0.0300	00	00	00	20	60	20
CLF F3	500	00	0.0125	00	00	20	60	20
CLF F4	500	00	0.0200	00	00	20	60	20
CLF F5	500	00	00	0.0350	00	20	60	20
CLF F6	500	00	00	0.0150	00	20	60	20

Evaluation of Clofibrate spherical agglomerates

Flow Properties

Pure Clofibrate and prepared spherical agglomerates were evaluated for bulk density and tapped density using density apparatus (TDA2, Campbell Electronics). The Carr's index and Hausners's ratio were then calculated by using ρb and ρt. The angle of repose was determined by fixed funnel method. [4]

Solubility Studies

The solubility of prepared spherical agglomerates was investigated, by adding the excess drug particles in the solvents and shaking the glass vials for specific time until reaching equilibrium conditions. A 0.45 µ-membrane filter solution was used to filter the solutions. UV-Spectrophotometer was used to determine the absorbance of the filtrate solutions after suitable dilution. The experiments were

undertaken at 25±0.1°C. The mean of three determinations was used to calculate the solubility of the drug in the solvents. [5]

Stability Studies

The selected formulation was evaluated for its stability at 40±2^{0}C/75±5% RH for about 2 months as per ICH guidelines. The samples were taken out after 3 months and evaluated for the drug content, solubility and *in vitro* release study. [6]

Results and Discussion

Flow Properties

These results confirm that spherical agglomeration drastically improved the flow and compaction behaviour of Clofibrate. All the findings were recorded in table 5.7

Table 2 Flow Properties of Clofibrate and prepared agglomerates

Formulation Code	Angle of repose	Hausner's ratio	Carr's index
Clofibrate	22.10^0	1.20	21.22 %
CLF F1	24.60^0	1.20	8.20
CLFF2	20.10^0	1.10	6.10
CLFF3	23.35^0	1.30	6.75
CLF F4	20.15^0	1.05	7.50
CLF F5	22.10^0	1.50	7.15
CLF F6	25.20^0	1.80	7.10

Solubility Studies

The mean of three determinations was used to calculate the solubility of the drug in the solvents. The obtained results were recorded in table 5.9.

Table 3 Solubility studies of Clofibrate and prepared agglomerates

Formulation Code	Solubility (µg/ml) in 0.1N HCl
Clofibrate	1113.10±50.10
CLF F1	2220.20±40.25
CLFF2	3265.50±20.20
CLFF3	3345.30±10.30
CLF F4	4212.15±10.30
CLF F5	4345.30±20.10
CLF F6	4480.10±20.20

Stability Studies

After 2 months of storage at accelerated storage condition, the prepared agglomerates formulation (CLF F2) doesn't show any significant different in results of drug content, solubility and *in vitro* release pattern, compared with zero time. This indicates the finalized formulation was quite stable.

Conclusion

The solvent diffusion technique (SDT) has changed into an operative technique to manufacture agglomerates of API crystals. Although, the planned technique showed benefits, such as cost effectiveness, that is considerably sensitive to the optimal of a stabilizer, which agonizes from an absence of systemic understanding in this field. In the existing study, the combination of different

solvents and stabilizers were equated to examine any connections between the solvents and stabilizers.

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