CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.322915

Available online at: http://www.iajps.com Research Article

ENHANCEMENT IN SOLUBILITY OF GLIBENCLAMIDE AND CLOFIBRATE DRUGS USING CARBOHYDRATE BASED NON-IONIC SURFACTANTS BY MICELLIZATION

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Received: 30 January 2017 **Accepted:** 8 February 2017 **Published:** 28 February 2017

Abstract:

The solubility enhancement process of hydrophobic drugs plays a key role in the formulation development to achieve the bioavailability and therapeutic action of the drug at the target site. As estimated, among the newly discovered chemical entities nearly 40% drugs are poorly water soluble. To get proper therapeutic level of drug in plasma, a high dose of poorly water soluble drugs is required. The orally administered drugs show its complete pharmacological effect if it is fairly soluble in water in gastric medium and such drugs show good bioavailability. The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development. Various methods are used to enhance the solubility of poorly water soluble drugs in aqueous medium. In this present study, surfactant micellization method was used to enhance the solubility of poorly water soluble drugs viz. glibenclamide, clofibrate. A carbohydrate based non-ionic surfactants, which was synthesized in lab, were explored to encapsulate these drugs. It was found that the water solubility of these drugs increased up to many folds.

Key Words: *poor water soluble drugs, bioavailability, carbohydrate non-ionic surfactant, clofibrate, glibenclamide, micellization*

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Please cite this article in press as Nirmal Singh and Lalit Sharma, ***Enhancement in Solubility of Glibenclamide and Clofibrate Drugs Using Carbohydrate Based Non-Ionic Surfactants by Micellization*** *, Indo Am. J. P. Sci, 2017; 4(02).*

INTRODUCTION:

Glibenclamide, a second generation sulfonyl-urea, is orally indicated in the treatment of type-II diabetes mellitus in patients whose hyperglycemia cannot be adequately controlled with diet and exercise. Glibenclamide also may be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks. Glibenclamide has, however, poor solubility in gastrointestinal fluid, leading to varying dissolution rate and incomplete or formulation-dependent bio-availability when orally administered [1-3]

To enhance the solubility of poor water soluble drugs, Solid dispersions method which include, the reduction of drug particle size to minimum followed by improving their wettability thus their bioavailability, was used [4]. The effect of cyclodextrins (CDs) on the solubility, dissolution rate, and bioavailability of cilostazol by forming inclusion complexes was studied [5]. The dissolution rate of glibenclamide was reported [6] to be significantly improved by preparing drug SDs using various preparation techniques and certain proportions of different carriers.

The solubility of Clofibrate a BCS class II Anti-hyperlipidemic drug belongs to fibrate class was enhanced [7] by formulation of solid dispersions by using various hydrophilic carriers, this improved its dissolution rate and oral bioavailability.

Biopharmaceutics Classification System (BCS)

The BCS is the scientific method to classify the drugs in various categories based on their aqueous solubility and intestinal permeability. This classification is based upon the tools that allow estimation of the contributions of three major factors, dissolution, solubility, and intestinal permeability that affect oral absorption of drugs. Out of the four different classes, BCS Class II and IV drugs, have low solubility, provide a number of challenges for formulation scientists working on the oral delivery of drugs[8].

In general, the term 'solubility' meant the maximum amount of solute that can be dissolved in a given amount of solvent. Solubility in quantitative terms is defined as the concentration of the solute in a saturated solution at a certain temperature [9]. The solubility of a solute in a solvent depends on the solvent used as well as on temperature and pressure[10]. Solubility varies over an extended range from infinitely soluble such as ethanol in water to poorly soluble such as silver chloride in water. The poorly or very poorly soluble compounds are often termed as insoluble [11]. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water [12]. For showing a pharmacological effect in the body and to get desired concentration of drug in the systemic circulation, solubility is one of the important parameter. The poor water soluble drugs generally require high doses to reach therapeutic plasma concentrations after oral administration. Most of the drugs are weakly acidic and weakly basic with poor aqueous solubility [13]. Drug release is an important and rate limiting step for oral bioavailability, particularly for drugs with low solubility and high permeability, i.e. BCS Class II drugs. By improving the drug release profile of BCS Class II drugs, it is possible to reduce the side effect of the drugs by enhancing their bioavailability [14]. The United States Pharmacopoeia and British Pharmacopoeia classify the solubility regardless of the solvent used, only in terms of quantification and have defined the criteria as given in Table 1[15] The BCS is a scientific framework for classifying a drug substance based on solubility, permeability, and dissolution criteria[16,17]. According to the BCS, drug substances are classified as follows:

Table 1: BCS classification of drugs

Class	Characteristics
Class I	High Permeability, High Solubility
Class II	High Permeability, Low Solubility
Class III	Low Permeability, High Solubility
Class IV	Low Permeability, Low Solubility

Table 2 : Terms of approximate Solubility according to USP [18]

Term	Part of solvent required for a part of Solute
Very soluble	Less than 1 part
Freely soluble	1 to 10 parts
Soluble	10 – 30 parts
Sparingly soluble	30 – 100 parts
Slightly soluble	100 – 1000 parts
Very Slightly Soluble	1000 – 10000 parts
Practically insoluble	≥ 10000 parts

Methods for Solubility Enhancement [19-21]

1. Physical modification
2. Chemical modification
3. Miscellaneous methods

1. Physical modifications

Particle size reduction: Drug particle size can be reduced by using micronization and nanosuspension techniques. Each technique utilizes different equipment for reduction of the particle size.

Micronization :

By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely on mechanical stress to disaggregate the active compound. Micronization of drugs is done by milling techniques using the jet mill, rotor-stator colloid mills, etc.

Nanosuspension (drug particles are stabilized by surfactants) :

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug which are stabilized by surfactants. Techniques for the production of nanosuspensions include homogenization and wet milling. Active drug in the presence of surfactant is defragmented by milling. Other techniques involve the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel, and buparvaquone.

2. Chemical modifications

Salt formation:

This is the most effective method of enhancing the solubility and dissolution rates of acidic and basic drugs, by converting them into their respective salts i. e. aspirin, theophylline, and barbiturates. Alkali metal salts of acidic drugs such as penicillins and strong acid salts of basic drugs such as atropine are water soluble than parent drugs.

Co-crystallization:

In this method, co-crystal is formed by complexation of two or more molecular species, which are held together by non-covalent forces. Only three of the co-crystallizing agents are classified and generally recognized as safe. It includes saccharin, nicotinamide, and acetic acid limiting the pharmaceutical application. It is an alternative to salt formation, particularly for neutral compounds.

pH adjustment :

By adjusting the pH, the hydrophobic molecule can be protonated (base) or deprotonated (acid) and be dissolved in water. Ionizable compounds that are stable and soluble after pH adjustment are best suited.

Co-solvency:

Cosolvents are mixtures of water and/or more water miscible solvent used to create a solution with enhanced solubility for poorly soluble compounds, e.g., of solvents used in the co-solvent mixture are PEG 300, propylene glycol, or ethanol. Dimethyl sulfoxide and dimethylacetamide have been widely used as cosolvent because of their large solubilization capacity of poorly soluble drugs and their relatively low toxicity[22].

Hydrotrophy :

Hydrotrophy, a term given by Neuberg [23] to describe the increase in the solubility of BCS Class 2 molecules in aqueous medium by the addition of high concentrations of alkali metal salts of various organic acids. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities.

Nanotechnology in pharmaceuticals:

Various nanonization techniques had been emerged to enhance the dissolution rates and bioavailability of number of poorly water soluble durgs and decrease systemic side-effects. Nanonization

broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. It is alternate to micronization because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution. There are different techniques used for nanonization of drug including wet milling, homogenization, emulsification-solvent evaporation technique, pear milling, and spray drying[24,25].

3. Miscellaneous methods

Super critical fluid technology:

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used either as a solvent for drug and matrix or as an antisolvent. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed.

Direct capsule filling:

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystalline nature of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique

MATERIAL AND METHODOLGY:

Material

Glibenclamide, Clofibrate (Sigma Aldrich, USA), distilled water, Ethanol (Nice chemicals pvt .ltd, Kerala), carbohydrate derived non-ionic surfactants (synthesized in lab, Shaheed Bhagat Singh State Technical Campus, Ferozepur, Punjab).

Methodology

Solubilization of poorly water soluble drugs using non-ionic gemini surfactants

carbohydrate based non-ionic surfactants (Figure 3) were explored as micellization probes for solubilization of poorly water soluble drugs like glibenclamide and clofibrate drugs under double beam UV monitoring (**Figure 1**).

The surfactants (5millimol) were shaken in water-ethanol mixture (20ml) at room temperature with poorly water soluble drugs (20mg) for 25 min and filtered. The filterate was extracted with double distilled n-hexane (2 x 10ml) solution, and the concentration of poorly water soluble drugs in n-hexane were determined by double beam spectrophotometer (299nm for Glibenclamide and 280 nm for clofibrate). Micellar ratio is determined as

Micellar ratio = $\frac{\text{concentration of entrapped drug molecule } (C_t)}{\text{concentration of surfactant } (C_s)}$

and $C_t = \frac{A}{\varepsilon l}$ in which A = absorbance

ε = molar extinction coefficient

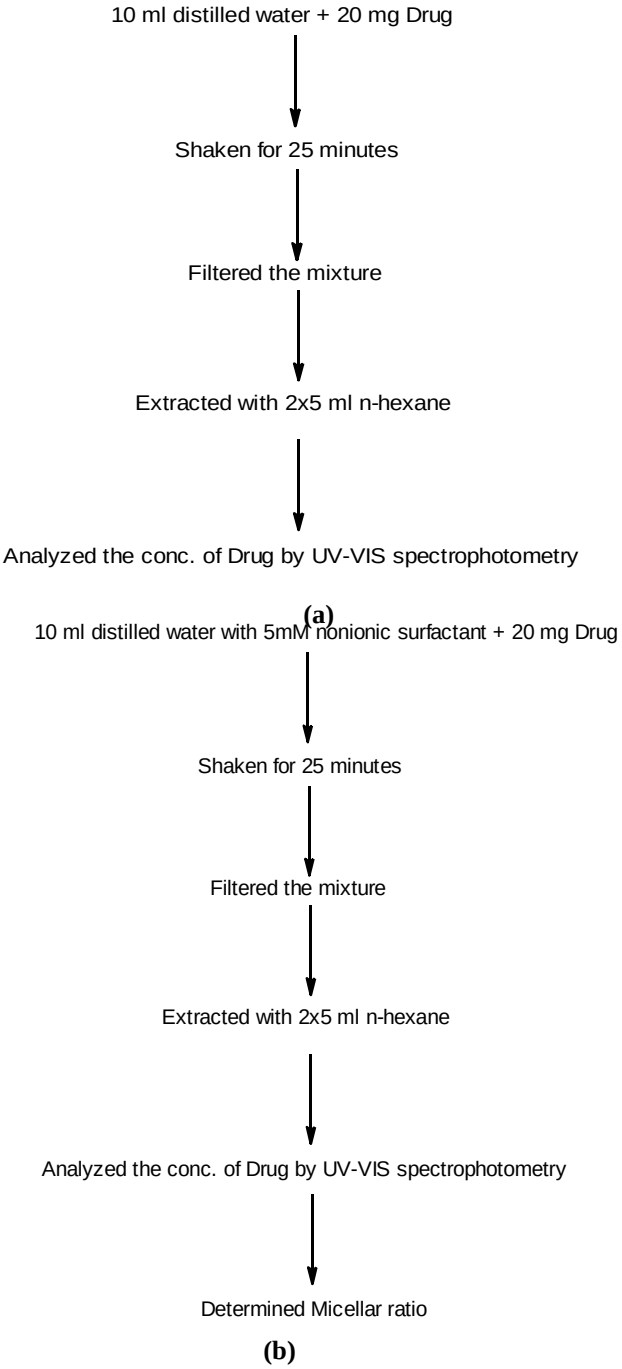


Fig. 1: (a) and (b) Flow chart for methodology for solubilization of poorly water soluble drugs

RESULT AND DISCUSSION:

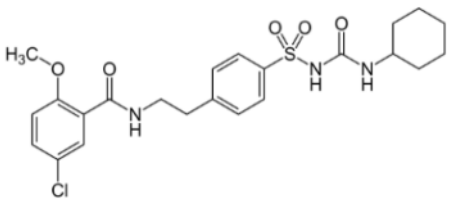
The carbohydrate derived non-ionic surfactants [26] were explored as micellization study for the solubilization of poorly water soluble drugs i.e. Glibenclamide and Clofibrate in water-ethanol system.

Table 3: Solubility of Glibenclamide in water: ethanol (90:10) with the help of micelle formed by surfactant

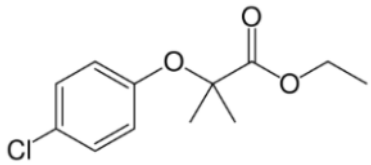
Surfactant	Micellar Ratio	Solubility of drug in presence of surfactant (mg/L)	Solubility enhancement
Nil	---	14.5	---
1	1:116	121.27	8.3
2	1:100.3	139.81	9.6
3	1:79.3	156.99	10.8

Table 4: Solubility of Clofibrate in water:ethanol system(90:10) with the help of micelle formed by surfactant

Surfactant	Micellar Ratio	Solubility of drug in presence of surfactant (mg/L)	Solubility enhancement
Nil	---	5.2	---
1	1:56	61.36	11.8
2	1:12.2	80.08	15.4
3	1:6.8	87.36	16.8

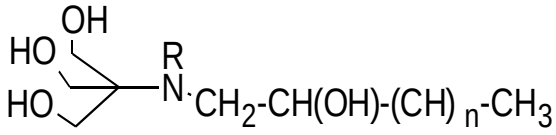


Glibenclamide



Clofibrate

Fig. 2: Structure of drugs used



1. n=9
2. n=11
3. n=13

R =

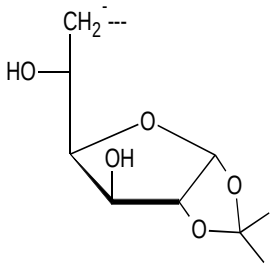


Fig. 3: Structure of carbohydrate derived non-ionic surfactant used for micellization [26]

The main driving force for encapsulation of drugs by non-ionic surfactants is the presence of carbohydrate moiety. As per study, the simple conventional surfactants without sugar moiety did not show any remarkable results. A sugar hydroxyl group interacts with the drug molecules in two ways. As a donor, it is responsible for free rotation of C-OH angle. This helps in the formation of linear bond with drug molecules. Hydrophobic portions on sugar surfaces and long alkyl tails contact the hydrophobic portions on drugs. Clofibrate is the most encapsulated moiety, followed by Glibenclamide. It is also found that the carbohydrate derived surfactants showed more efficiency to encapsulate poorly water soluble drugs as compared to non-sugar surfactants. Micellar system can also be used to encapsulate poly aromatic hydrocarbons (PAHs) in n-hexane.

CONCLUSION:

The above investigation show that the solubility of poorly water soluble drugs viz. Glibenclamide and Clofibrate, was enhanced many folds by micellization in the presence of carbohydrate derived non-ionic surfactants. The aqueous solubility of Glibenclamide was enhanced 10.8 times and that of clofibrate was enhanced about 16.8 times (**Tables 3 and 4**). Micellar studies revealed that these carbohydrate derived non-ionic surfactants encapsulated drugs in the sequence Clofibrate > Glibenclamide. In all cases, aqueous solubility increased with increase in chain length of the surfactant.

ACKNOWLEDGEMENT

We are grateful to Department of Science and technology, New Delhi (grant SERC/OC-17/2006) for financial support.

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