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"Solubility Study Of Formoterol Fumarate Dihydrate, Glycopyrrolate And Budesonide Drugs As A practical Tool For Analytical Method Development"

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***Abstract*—**
All Drug molecules are Differ in their physical and Chemical properties. Any analytical method development will start with literature search and then the first practical step is to perform solubility analysis of drug which will be used as a basic information in Analytical method development for analysis of Different drugs in Different dosage forms. Here We selected Formoterol Fumarate Dihydrate, Glycopyrrolate and Budesonide drug molecules which are mainly used for treatment of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and Asthma. Solubility analysis gives us information about type of chromatography can be used either Normal phase or Reverse phase. It also helps for Mobile phase and diluent selection for cost effective analytical method development. Water is a Universal solvent and Acetonitrile and Methanol are cheap and widely used solvents in Pharmaceutical industry. So, Here Water, Methanol and Acetonitrile solvents are used for the solubility study.

Keywords— Solubility, Analytical method development, Metered dose inhalers, Dry powder inhaler, Chromatography.

I: INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease. It is characterized by long-term breathing problems and poor airflow. The main symptoms of COPD include shortness of breath and cough with sputum production. COPD is a progressive disease, meaning it typically worsens over time. The term "chronic bronchitis" is also used to define a productive cough that is present for at least three months each year for two to three years. Formoterol Fumarate Dihydrate (Chemical name : Fumaric acid; N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4- methoxyphenyl)-1-methyl-ethyl] amino] ethyl] phenyl] formamide; dihydrate, Molecular weight = 840.92), Glycopyrrolate (Chemical name : 3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1- dimethylpyrrolidinium bromide, Molecular weight = 398.34) and Budesonide (Chemical name : 11β,21-dihydroxy-16α,17α-(butylidenebis(oxy))pregna-1,4-diene-3,20-dione, Molecular weight = 430.53) drug molecules are mainly used in different combinations in multiple Aerosol dosage forms to treat COPD, Asthma and Chronic bronchitis. All three drugs are available in white to almost white powder form.

Drug molecules Formoterol Fumarate Dihydrate, Glycopyrrolate and Budesonide are selected to study the solubility of these three drugs and data generated from this study will be helpful for further analytical method development of different aerosol dosage forms containing different combinations of these drugs.

Aerosol dosage form has many advantages over the classical pharmaceutical dosage forms. Dry powder inhaler and metered dose inhalers are administered with mouth or nose and reaches directly to the lungs of patients to give desired local effect. It does not required to go into systemic circulation and so gives very fast relief. These dosage forms are mainly anti asthmatics and requires very low dose ranging from 5 mcg to 400 mcg per dose. So method development for analysis of these drugs is very challenging job.

II: MATERIALS

Formoterol Fumarate Dihydrate working standard used for this is manufactured by Harman chemicals limited, Glycopyrrolate working standard used for this study is manufactured by Vamsi labs limited and Budesonide working standard used for this study is manufactured by Aarti industries limited. These standards are provided for method development by Zydus Cadila Healthcare Limited, Ahmedabad, India and Study performed at pharmaceutical technology centre, Analytical development laboratory of Zydus cadila healthcare limited.

III: SOLUBILITY ANALYSIS

Solubility can be easily said as the ability to be dissolved. In scientific term solubility can be defined as the amount of (solid substance) solute will dissolve in a particular amount of a solvent (Liquid substance). Solubility is expressed in terms of g/L (grams of solute per litre of solution).

Solubility analysis is done for the selection of right solvent in Analytical method development. Here, solubility is determined by using different solvents like Water, Acetonitrile, and Methanol.

In British pharmacopeia several terms are defined from Very soluble to practically insoluble to give exact idea of solubility of solute in any solvent.

For e.g. If 1 gm Formoterol Fumarate Dihydrate is dissolved in about 40 mL of Acetonitrile then it can be defined as Formoterol Fumarate Dihydrate is sparingly soluble in Acetonitrile.

The reference table which is given in British pharmacopeia is tabulated below.

Table - I: Solubility (reference source: British pharmacopeia General notices part-3)

Term	Approx. volume of solvent per gram of solute (mL)		
Very soluble	less than	1	
Freely soluble	From	1	10
Soluble	From	10	30
Sparingly soluble	From	30	100
Slightly soluble	From	100	1000
Very slightly soluble	From	1000	10000
Practically insoluble	More than		10000

IV: PROCEDURE FOR SOLUBILITY

A 10 mL volumetric flasks taken, labelled the flask with name solubility of Formoterol Fumarate Dihydrate in water. An accurately weighed quantity of Formoterol Fumarate Dihydrate working standard about 100 mg transferred to the same flasks. Exactly 0.1mL of HPLC grade water added to it with help of graduated pipette and checked that if drug becomes soluble or not. Further added 0.4 mL (0.1 mL + 0.4 mL=0.5mL) of water to it and checked for solubility. Data were generated for solvents Methanol and Acetonitrile by taking same amount of Formoterol Fumarate Dihydrate in different 10 mL volumetric flasks.

Same way data generated for Glycopyrrolate and Budesonide drugs in different solvents by taking 100 milligrams of weight of each substance for each solvent like Water, Methanol and Acetonitrile. The observations are tabulated in following tables.

Table-II: Solubility data of Formoterol Fumarate Dihydrate in Water, Methanol and Acetonitrile

mL of solvent added	Soluble in Water	Soluble in Methanol	Soluble in Acetonitrile
0.1	No	No	No
0.5	No	No	No
1.0	No	No	No
1.5	No	No	No
2.0	No	No	No
2.5	No	No	No
5.0	No	Yes	Yes
10.0	No	Yes	Yes

Table-III: Solubility data of Glycopyrrolate in Water, Methanol and Acetonitrile

mL of solvent added	Soluble in Water	Soluble in Methanol	Soluble in Acetonitrile
0.1	No	No	No
0.5	No	No	No
1.0	Yes	Yes	Yes
1.5	Yes	Yes	Yes
2.0	Yes	Yes	Yes
2.5	Yes	Yes	Yes
5.0	Yes	Yes	Yes
10.0	Yes	Yes	Yes

Table-IV: Solubility data of Budesonide in Water, Methanol and Acetonitrile

mL of solvent added	Soluble in Water	Soluble in Methanol	Soluble in Acetonitrile
0.1	No	No	No
0.5	No	No	No
1.0	No	No	No
1.5	No	No	No
2.0	No	No	No
2.5	No	No	No
5.0	No	Yes	Yes
10.0	No	Yes	Yes

V: LIMITATION OF STUDY

The drug molecules Formoterol Fumarate Dihydrate, Glycopyrrolate and Budesonide are very expensive materials, therefore it is not advisable to use 1 gram of substance for solubility analysis for each solvent. So, for this study we were used 100 milligrams of each substance for to check solubility in each solvent.

VI: RESULTS AND DISCUSSION

The above data shows that the Formoterol Fumarate Dihydrate is sparingly soluble in Methanol and Acetonitrile. Glycopyrrolate is Soluble in all three solvents Water, Methanol and Acetonitrile. Budesonide is sparingly soluble in Acetonitrile in Methanol.

VII: CONCLUSION

Based on above data it can be concluded that all three drug molecules Formoterol Fumarate Dihydrate, Glycopyrrolate and Budesonide are suitable for analytical method with Reverse phase chromatography. It can also be concluded that The mobile phase and diluent can be prepared in different appropriate ratios of Water, Methanol and Acetonitrile for desired elution of Formoterol Fumarate Dihydrate, Glycopyrrolate and Budesonide drugs.

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