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Review Article

Microwave energy a novel approach in solubility enhancement: A review

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ABSTRACT

The development of any pharmaceutical dosage forms starts with the Preformulation studies; Preformulation studies focuses on the physicochemical properties of drug candidate that could affect the drug performance and can define various critical attributes in development of potential dosage form. Out of the various parameters considered in Preformulation studies, solubility remains the most important aspect when it comes to the lower bioavailability of the drug candidate. Out of the all NCE's 40% of the drug candidates lacks the solubility which potentially accelerate the need of solubility enhancement of the drug. Many attempts and practices have made in order to increase solubility of the drug which involves use of certain organic solvents, some mechanical processes, Co-solvency approach etc. Green chemistry is a sustainable chemistry which is used in product or processes that will eliminate the use and generation of hazardous products. Microwave technique generally required no use of any solvents or any mechanical process, in this review article an attempt was made to enlighten the potential use of microwave technique which can be utilized in pharmaceutical industry.

Keywords: Preformulation, Solubility, Microwave technique, solid dispersion, Green chemistry.

INTRODUCTION

Preformulation studies were evolved in 1950 and 1960. Preformulation testing is the first step in the rational development of dosage form of the drug substances. Preformulation, is group of studies that focuses on the physicochemical properties of the new drug candidate that could affect the drug performance and development of dosage form. There are numbers of physicochemical characters which are studied in the Preformulation stage. Some of them which include organo-leptic characteristics, bulk characterization, compressibility, hygroscopicity, drug-Excipient compatibility, flow properties etc. Out of all the characteristics which remain the predominant character to study, is solubility analysis of the compound [1]. Solubility of the drug is the most difficult aspect in formulation and development. Solubility of the drug is the most effective barrier in bioavailability thus increasing the solubility we can achieve the optimum level of drugs in systemic

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circulation and also minimize the side effects associated with lower solubility of the drug. Drug having poor solubility are more prone to lower absorption and inadequate bioavailability, resulting in the need of higher dosage to achieve desired therapeutic concentration [2].Various methods which are available to increase the solubility of the compound require some physical and chemical modification of the compound, or involve use of various organic solvents which also increases the cost of the procedure and also increases the involvement of hazardous solvents and treatment. Microwave irradiation is relatively a novel method for solubility and dissolution enhancement of poorly soluble drugs. MW equipment depends on the use of the electromagnetic waves between the radio and infrared frequencies over the range between 0.3-300GHz. These waves travel within the material causing the oscillation of the molecule and thus generating the heat within the sample. MW differs from the conventional heating due to its ability to heat the sample at any point of time. In MW the heat is generated inside the material and then passes to entire volume with constant heating rate.MW have the ability to penetrate any material leading to heat production everywhere in the material at the same time.MW is the green, clean and cost effective approach for the solubility enhancement[3].

SOLUBILITY AND ITS IMPORTANCE

Aqueous solubility is one of the major challenges in the early stages of drug discovery and any attempt to increase the solubility is the great importance in the pharmaceutical industry. Before a drug becomes available to the site of action or its receptor it has to cross the barrier of biological fluids. Out of the NCE's 40% of the drug candidate have to problem of lower solubility. Solubility is defined as the maximum quantity of a drug dissolved in given volume of a solvent/solution. Aqueous solubility has an essential role in bioavailability of oral drug formulations. The classification given by USFDA defines the drugs according to their permeability and solubility as described in Table 01& Table 02 respectively.

The BCS classification correlates the in vitro permeability and solubility to in vivo bioavailability. Class I drugs are with oral bioavailability being limited by their ability to reach the absorption site. Class II drugs are poorly water soluble but are able to permeate through GI tract. Class III drugs are soluble but having the permeability issues and their oral bioavailability is limited by barrier properties of the of GI tract, whereas class IV drugs faces both the problems of solubility and permeability. [4]. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance and industrial acceptance and cost-effectiveness, and flexibility in the design of the dosage form. However the major challenge with the design of oral dosage forms of the compound is its bioavailability which is totally depends on the solubility of the compound. Solubility plays a major role in dosage form design. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation [5]. General definitions for different solubility terms are as depicted in Table 03[6].

Solubility Enhancement Techniques

The solubility of a solute is the maximum quantity of solute that can dissolve in certain quantity of solvent or quantity of solution at specified temperature. Various techniques which are available to improve the poorly soluble drugs, the techniques which are reported for the solubility enhancement of poorly water soluble drugs are given in Table 04 [7-9].

The poor solubility of drug/drug candidate could be overcome by using solubility enhancement technique including as stated in Table 04. All the techniques show some kinds of disadvantage which potentiates the need of a novel technique for solubility enhancement of the drugs and NCE's. The various types of technique which faces some kinds of disadvantages are given in Table 05. [10].

Due to above stated problems in various technique there is a need of a technique which will overcome the problems and also will be the simplest, Cost effective, green and clean. Green chemistry which is the latest and one of the most researched topics now days has been in demand since 1990's. Green chemistry as it names indicted involves the environmental friendly and cost effective utilization of resources that minimize or even eliminate the production of harmful bi-products in design and manufacturing of the products.[11]

PRINCIPLES OF GREEN CHEMISTRY:

Paul Anastas and John C. Warners explained the principles which form the basis of green chemistry. According to them green chemistry is:

- To design and development of such processes which maximize the conversion of raw material to products so that maximum yield of product is obtained.
- To implement the usage of such substance which are environment friendly or substance which are derived from environmental including solvents
- Designing of energy efficient processes.

Green chemistry generally involves use of aqueous hydrogen peroxide, super critical carbon dioxide as

a green solvent and microwave radiation as a replacement of conventional heating measures Microwave induced processes are important tools in green chemistry[12].Microwave irradiation the most prominent tool in green chemistry is a well known method for heating and drying materials microwave having the ability to penetrate the substances, allow the production of heat in any point of the sample at the same time. In fact microwave radiation offers several advantages such as rapid volumetric heating, no overheating at the surface, higher yields and energy saving. Microwave in the form of electromagnetic energy which lies in electromagnetic spectrum corresponds to frequency of 30GHz to 300MHz.Microwave energy consists of electrical and magnetic field. Microwave energy moves with the speed of light and it have very less energy relative to energy which is required to break the bond in chemical molecule thus microwave are such a source of energy which will not hamper the structure of chemical molecule.[13-14]

PRINCIPLES OF MICROWAVE HEATING [15]

In the electromagnetic spectrum the microwave region is located between infra-red region and radio-waves regions. The basic difference between conventional means of heating and microwave heating is conventional heating first react with the reaction vessel, the reactant are slowly activated by external sources Heating is driven into substance, passing through walls and then reach up to reactant as described in Fig.01. In microwave heating there is a direct coupling of between molecules takes place which leads to rapid rise in temperature and causing instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conductivity. The acceleration of chemical reaction by microwave exposure results from the interaction between the material and electromagnetic field leading to thermal and specific effects. For microwave heating the substance must possess a dipole moment. A dipole is sensitive to external field and tries to align itself with the field by rotation. If submitted to an alternating current , the electric field is inversed at each alternate and therefore dipole tend to move together to follow the inversed electric field Such a characteristic induces rotation and friction of molecule, which dissipates as internal homogeneous heating. The electric field of commonly used irradiation frequency (2450 MHz) oscillates 4.9 x 109 times per seconds thus microwave heating is directly dependant on dielectric properties of substance, dielectric constant(ε') and dielectric loss (ε"). The ability of material to convert electromagnetic energy into heat at given frequency and temperature is calculated using

$$\varepsilon'' / \varepsilon' = \tan \delta \quad (1)$$

Where, δ is the dissipation factor of the sample

ε'' is dielectric loss which measure the efficiency with which heat is generated from electromagnetic radiation

ε' is dialectic constant which gives the ability of molecule to polarized by an electric field.

MICROWAVE HEATING IN SOLUBILITY ENHANCEMENT TECHNIQUE[16-19]:

The microwave heating can be applied for enhancement of solubility rate of Pioglitazone by solid dispersion with Poloxamer 188 prepared by microwave irradiation method. 11.46 fold increases in solubility of Pioglitazone was observed when compared to physical mixture. Pioglitazone was converted into amorphous forms in solid dispersion which is mainly responsible for solubility and dissolution enhancements. The FT-IR, DSC and PXRD study supports the claim of conversion of Pioglitazone into more soluble amorphous form. Racecadotril is an ant diarrheal drugs, an attempt was made to increase the solubility and dissolution rate of the RAC. Result obtained from DSC, PXRD confirmed the conversion of crystalline to amorphous form of RAC which results in solubility enhancement of drug. Significant decrease in drying time was obtained by microwave irradiation. FTIR and TLC studies show no degradation in the RAC. Solid dispersion of Meloxicam and Poloxamer was made by using hot melt and microwave assisted method. The microwave assisted method was found to be better than melting method for preparing solid dispersion. The possibility of preparing an Nano-composites of atorvastatin calcium by microwave assisted technique. The study successfully demonstrated the use of Acacia gum, Modified gum karaya, PVP K-30 as carrier for the formation of microwave generated NC's in the solubility and dissolution enhancement of atorvastatin calcium TheFTIR, XRC and DSC studies concluded that the drug has been converted to Nano-crystals in the composites and this way responsible for solubility enhancement. An increase in hypolipidemic effect was reported after pharmacological evaluation. Thus stated method was regarded as novel and commercially feasible technique for improving the in-vitro and in-vivo performance of atorvastatin calcium.

Advantages and disadvantages of microwave energy [20]

- Rapid volumetric heating
- No overheating at the surface
- Better and rapid process control
- High heating efficiency
- Uniform heating occurs throughout the material as opposed to surface and conventional heating process
- Increased process speed

- Floor space requirement are decreased
- Improved reproducibility
- Reduce wastage and formation of bi-products
- Selective heating
- Low operating cost
- Elimination of formation of hazardous products
- Environmental heat loss can be avoide.

Disadvantages of microwave technique:

- It is very difficult to set proper temperature for reaction to occur
- Microwave oven method cannot be applied for heat sensitive material

MICROWAVE HEATING AND ITS OTHER APPLICATIONS

Microwave technology has been successfully applied for processing of various foods various industries. The microwave pasteurization and sterilization of foods have claimed to effectively destroy pathogenic microorganism and reduce the processing time without the damage to quality of the product. The microwave hating applied for food process such as blenching, cooking and baking have the advantage of retaining more taste color quality and nutritional values and has great effect on preservation. Microwave energy also provides the advantages such as reduced processing time, cost-effectiveness, increase thermal efficiency, reduction in drying time and higher rehydration capacity. The microwave energy can also be beneficial in cement and concrete industries. The application can include cement synthesis, accelerated curing, decommissioning of decontaminated concrete, nondestructive monitoring and concrete drilling/melting.[21-22].

Conclusion

The microwave energy is claimed to be as source of safe, effective and non-hazardous technique which can be applied in numerous industries. In pharmaceutical industry the energy can successfully applied for enhancement of dissolution rate and to increase the solubility of the various poorly water soluble drugs with minimum interaction with the drug and Excipient. Also the method can be applied for the food processing, pasteurizing and sterilization of the eatables, the microwave can be found beneficial in the cement and concrete industries also. Hence the microwave energy can be applied to the fullest potential in various industries.

Conflict of interest: There is no conflict of interest.

TABLE 1: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

Biopharmaceutcal classification system		
Class	Permeability	Solubility
Class I	High	High
Class II	High	Low
Class III	Low	High
Class IV	Low	Low

TABLE 2: BCS CLASS OF DRUGS AND EXAMPLE OF EACH CLASS

Biopharmaceutical classification system (BCS) of drugs and example of each class		
	High solubility	**Low solubility**
High permeability	Class I	Class II
	Acetaminophen	Flubiprofen
	Caffieine	Warfarin
	Prednisolone	Carbamazepine
	Diazepam	Phenytoin
Low permeability	**Class III**	**Class IV**
	Acyclovir	Acetazolamide
	Allopurinol	Azathioprine
	Atenolol	Chlorthiazide
	Captopril	Mebendazole

TABLE 3: DEFINITION OF SOLUBILITY

Definition	Parts of solvent required per part of solute in (ml)
Very soluble	Less than 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10,0000
Practically insoluble	10,000 and more

TABLE 4: SOLUBILITY TECHNIQUES

Various solubility enhancement technique			
Chemical modification	**Physical modification**	**Comlexation**	**Inclusion complex technique**
Salt formation	Particle size reduction	Physical mixture	Lyophilization
Co-crystallization	Micronization	Kneading method	Microwave irradiation
Co-solvency	Nanosuspension	Co-precipitate method	----
Hydrotrophy	----	-----	----
Nanotechnology			

TABLE 5: PROBLEMS IN SOLUBILITY ENHANCEMENT TECHNIUQE

Method	Problems associated with techniques
Co-solvency approach	• Toxicity and tolerability related with the level of solvent administered has to be considered • Many of the insoluble compounds are unsuited to cosolvent
Nanotechnology	• The agglomeration problem is inherent and difficult to overcome
Particle size reduction	• Due to high surface charge on discrete smll particle there is strong tendency for particle agglomeration • Physical mechanical stress may induce degradation of ctive compound
Micronization	• High energy process which cause disruption in drug crystal lattice • Amorphous regions re thermodynamically unstable and susceptible to recrystallization
Nanosuspension	• Suffer from problem of instability due to agglomeration growth called Ostwald ripening
Lyophilization	• Use of specialized equipment • Time consuming process

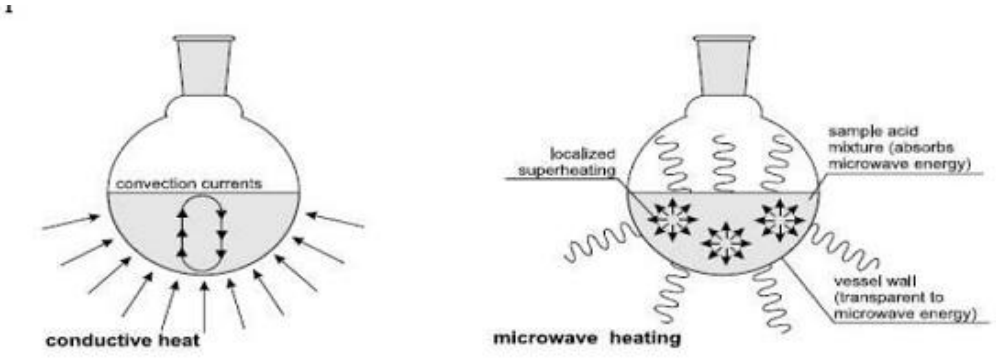

Figure 1: Difference in conventional heating and microwave heating

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