ENHANCING THE DISSOLUTION AND SUSTAINING THE RELEASE OF DICLOFENAC SODIUM USING THE METHOD LIQUISOLID TECHNOLOGY

A thesis submitted to the School of Graduate Studies of Addis Ababa University in partial fulfillment of the requirements for the Degree of Master of Science in Pharmaceutics

By:-Lidia Tesfaye (B. Pharm)

Under the supervision of Prof. Tsige Gebre-Mariam and Dr. Anteneh Belete, Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, Addis Ababa University

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ABSTRACT

Various methods of modifying solubility and dissolution properties of drugs have been developed over the years. Methods such as liquisolid technology, which can be used to enhance or sustain dissolution, have raised a lot of interest in many researchers. In this study different liquisolid compacts of diclofenac sodium containing either propylene glycol or polyethylene glycol 400 for the enhanced dissolution preparations; and Polysorbate 80 as a non-volatile solvent for sustained preparation were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. Microcrystalline cellulose, colloidal silica and sodium starch glycolate were employed as carrier, coating material and disintegrant, respectively. Formulation of liquisolid compacts having various ratio of carrier to coating material (ranging from 10 to 30) and 50 to 70% concentration of liquid medication (drug:non-volatile solvent) were prepared and evaluated for their powder, tablet property and drug release profile. The liquisolid compacts demonstrate considerably higher dissolution rate than marketed tablets. This was due to increased wetting properties and surface of drug available for dissolution. Also it has been shown that the fraction of molecularly dispersed drug in the liquid medication of liquisolid system was directly proportional to the dissolution rate and the percentage drug dissolved in 10 minute was correlated with solubility of the drug in different vehicle. A plot of the percentage drug dissolved against the solubility of diclofenac sodium showed that the amount of drug dissolved increased linearly with an increase in solubility of diclofenac sodium in the vehicle. Diclofenac sodium tablets prepared by liquisolid technique also showed release retardation properties. This study revealed that Polysorbate 80 and Eudragit® RL has important role in sustaining the release of drug from liquisolid matrices. It is generally proven that liquisolid technique is a promising alternative as a tool to enhance or sustain the release of diclofenac sodium.

Key words: Liquisolid compact, Diclofenac Sodium, Solubility, Dissolution, Sustained release.

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ACRONYMS

Φ value	Flowable liquid retention potential
Ψ value	Compressible liquid retention potential
BCS	Biopharmaceutical classification System
CI	Carr's index
DR	Dissolution rate
DS	Diclofenac sodium
ERLSC	Enhanced release liquisolid compact
f2	Similarity factor
FM	Fraction of molecularly dispersed drug
HR	Housner's ratio
HPMC	Hydroxypropyl methyl cellulose
Lf	Liquid load factor
LSC	Liquisolid compact
LSF	Liquisolid flowability
MCC	Microcrystalline cellulose
NSAID	Non-steroidal anti-inflammatory agent
PEG	Polyethylene glycol
PG	Propyleneglycol
PVP	Polyvinylpyrolidine
R value	Ratio of carrier to coating material
SRLSC	Sustained release liquisolid compact
SSG	Sodium starch glycolate
Tg	Glass transition temperature

OPERATIONAL DEFINITION

As used herein, the following terms have the meaning described below unless otherwise indicated [Spireas *et al*., 1998]:

The term "liquid medication" includes liquid lipophilic drugs and drug suspensions or solutions of solid water-insoluble drugs in suitable non-volatile solvent systems.

The term "liquisolid systems" refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water-insoluble solid drugs in suitable non-volatile solvent systems, into "dry" (i.e., dry-looking), nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules that are prepared using the technique described under "liquisolid systems," combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for immediate or sustained release action, such as disintegrants or binders, respectively.

The term "flowable liquid-retential potential" (Φ-value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ-value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture.

The term "compressible liquid-retential potential" (Ψ-number) of a powder material describes its ability to retain a specific amount of liquid while maintaining good compression properties. The Ψ-number is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably compressible liquid/powder admixture, i.e., being able to yield tablets of satisfactory mechanical crushing strength (hardness) without presenting any liquid squeezing out of the liquisolid mass during compaction.

The term "carrier material" refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

The term "coating material" refers to a material possessing fine and highly adsorptive particles, such as various types of amorphous silicon dioxide (silica), which contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid. These adsorptive particles have a particle size range of about 10 nm to 5,000 nm in diameter.

The term "tablet property" refers to those attributes of the compact that are studied after the tablet compressed. These are hardness, friability, content uniformity and weight variation. Drug release profile of the compact is treated independently.

The term "Powder property" refers to those attributes of the liquisolid system that are studied from the liquisolid powder prepared. In this study the flow of the powder was studied using HR CI and angle of repose. Angle of repose was used as a major variable for comparing the formulation for their flow property.

The term "R val;ue" also named as the powder exicipent ratio, is the fraction of weight of carrier (Q) and the coating material (q) present in the formulation R= Q/q.

The term "Lf value" is defined as the weight ratio of the liquid medication (w) and carrier powder (Q) in the system (Lf= w/Q) which must be posed by an acceptable flowing and compressible preparation.

The term "Hydrophobic carrier" refers to those carriers such as Eudragit RL and RS, HPMC K4M etc, for sustained release.

The term "Non-Volatile solvents" refers to preferably water-miscible, Inert high boiling point and not highly viscous organic solvent systems such as propylene glycol, liquid polyethylene glycols, N, N dimethylacetamide, polysorbates, glycerin, fixed oils etc., are most suitable as vehicles

1. INTRODUCTION

An estimated 40% of the newly developed molecules have poor water solubility, which lead to poor bioavailability and high dropout rate from the drug discovery and development process [Gupta *et al*., 2011]. About 15% of the drug-like compounds and 40% of lead optimization compounds are insoluble at a concentration less than or equal to 20 μg/ml. These drugs tend to be eliminated from the gastrointestinal tract before they fully dissolve and be absorbed into the blood circulation. As about 70% of the human body is made up of water, a drug must be water-soluble and thus possess an acceptable bioavailability level [Allam *et al*., 2011; Patel *et al.,* 2010].

Traditionally compounds were considered to be poorly soluble if their solubility were less than 100μg/ml. In 2006 Fligge and Schuler redefined the concept of poor solubility; a compound is poorly soluble when the solubility is less than 20 μg/ml, partly soluble when the solubility is 20-80 μg/ml and soluble when the solubility is over 80 μg/ml [Saharan *et al*., 2009a; Saharan *et al*., 2009b]. According to Biopharmaceutical Classification System (BCS), there are four classes of drugs. In the first class, drugs with high permeability and solubility are included. They are formulation independent. That is, their bioavailability is determined only by delivery of the drug solution to the intestine. Benzapril, Loxoprofen and Sumatriptan are included in this class. Class II drugs are highly permeable but with low solubility. The bioavailability of compounds in this class is limited by drug solubility/dissolution (Formulation dependent). Some of the drugs in this class are Valsartan, Nimesulide, Loratadine and Diclofenac. Class III drugs are characterized by low permeability but high solubility. The bioavailability of these drugs such as Gabapentine and Atropine is limited by intestinal permeability only. Class IV (Hydrochlorthiazide, Furosemide, Meloxicam) is characterized by low permeability and low solubility [Amidon *et al*., 1995; Zaheer *et al*., 2011].

The solubility or dissolution of a drug substance can be mainly altered on two levels, through material engineering of the drug substance or through formulation approaches [Stegemanna *et al*., 2007].The formation of water soluble molecular complexes, drug micronization, solid dispersion, co-precipitation, lyophilization, microencapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the

major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs, however, among them, the technique of ‘‘liquisolid compacts” is one of the most promising technique which can also be used to sustain drug release [Saharan *et al*., 2009a; Kulkarni *et al*., 2010].

The first common method is particle size reduction; but aggregation of the micronized drug as a result of their hydrophobicity and electrostatic charge and reducing their available surface area is its limitation. The other method is drug adsorption on hydrophilic silica aerogels which is dependent on the selected drug and only low drug loads are achieved and it involves complex manufacturing process. In complexation of a lipophilic drug with cyclodextrin, the maximum possible drug load is relatively low and the inclusion complexation only works with drugs that fit into the cavities of the cyclodextrin molecule. Solid dispersion is one of the common methods however for the preparation of solid dispersions usually special equipment is needed such as a spray dryer or a fluid bed apparatus and it is difficult for large scale production [Vemula *et al*., 2010; Sharma and Jain, 2010].

1.1 Liquisolid Compact

1.1.1 Historical development

Historically, liquisolid compacts (LSC) are descendants of ‘powdered solutions’, an older technique which was based on the conversion of a solution of a drug in a non-volatile solvent into a dry-looking, non adherent powder by mainly adsorbing the liquid onto silica of large specific surfaces [Sambasiva and Naga, 2011]. Such preparations, however, have been investigated for their dissolution profiles while being in a powder dispersion form and not as compressed entities, simply because they could not be compressed into tablets (‘liquid squeezing out’ phenomena and unacceptably soft tablets) [Satheeshbabu *et al*., 2011].

Liquisolid compacts, on the other hand, are acceptably flowing and compressible powdered forms of liquid medications, and have industrial application. In addition, the term ‘liquid medication’ does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions, or liquid oily drugs. Therefore, in contrast to

'powdered solutions', the term 'liquisolid compacts' is more general [Nagabandi *et al*., 2011]. The new 'liquisolid' technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insoluble solid drugs carried in non-volatile liquid vehicles) into dry, non-adherent, free-flowing and compressible powder mixtures suitable for tableting or encapsulation. In addition to enhancing the dissolution the method could be modified to sustain the release from the compact [Spireas, 1998].

1.1.2 The theory behind the technique

In liquisolid compact of Spireas *et al.*,(1998), when drug candidate is dissolved in a non-volatile liquid vehicle and incorporated into carrier material having porous structure and closely matted fibers in its interior, a phenomenon of both adsorption and absorption occurs [Gubbi and Jarag, 2009]. This implies that the drug in the form of liquid medication is absorbed initially in the interior of particles of carrier and after saturation of this process it gets adsorbed into internal and external surfaces of carrier. Finally, as depicted in figure 1.1 coating materials such as amorphous silica which have high adsorptivity and greater surface area lead to the liquisolid systems desirable flow properties [Fahmy and kassem, 2008].

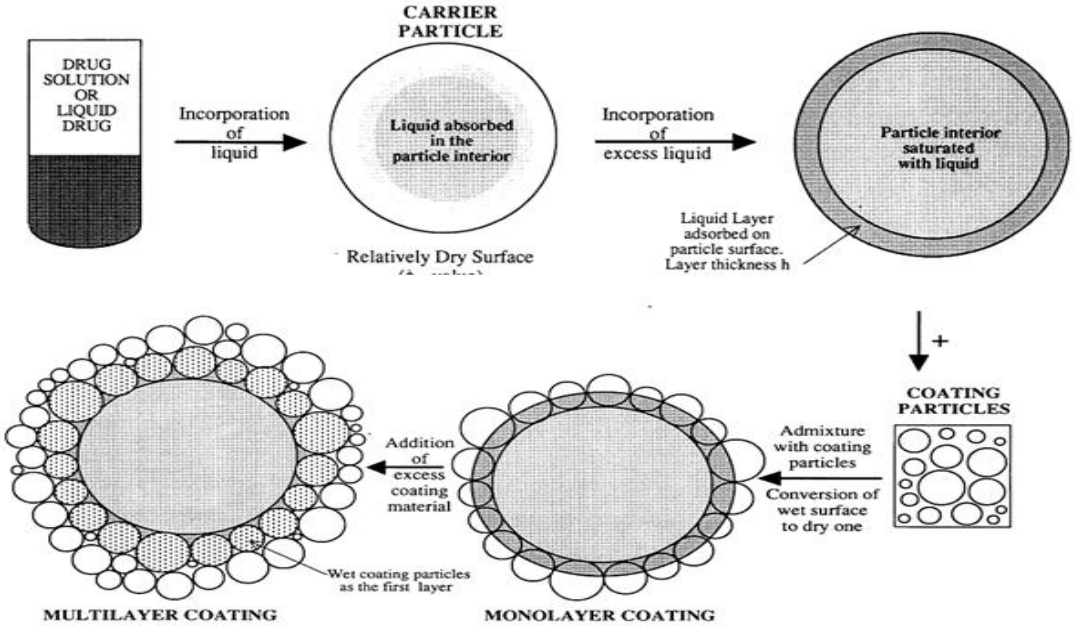

Figure 1.1: Scheme depicting the formulation process of liquisolid system [Sambasiva and Naga, 2011]

1.1.3 Approaches to enhance dissolution

Three ways were proposed to increase dissolution of the drug from the LSC. Increased drug surface area is the first one. The drug within the liquisolid system is completely dissolved in the liquid vehicle and also located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within conventional tablets [Singh *et al*., 2011; Khalid *et al*., 2010].

The relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium, it is possible that the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co solvent [Karmarkar *et al*., 2010b].

The third approach will be due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension; wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles [Javadzadeh *et al*., 2007a].

1.1.4 Approaches to sustain drug release

It is suggested that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. This can be achieved by different strategies; selection of appropriate solvent, using hydrophobic carrier, increasing the amount of coating agent (low R value) and utilizing other retarding agent such as Hydroxypropyl methylcellulose (HPMC) [Javadzadeh *et al*., 2008; Spireas and Bolton *et al*., 1998].

There are several researches done on liquisolid formulations with sustained drug release containing hydrophobic carriers such as Eudragit® RL or RS instead of hydrophilic carriers, the latter being used for fast release liquisolid formulations. Hydrophobic carriers may lead to poor wetting properties of the compacts resulting in slow disintegration and thus, prolonged drug release [Ganesh *et al*., 2011].

It was shown that the liquid vehicle may act as a plasticizer and thus, decreases the glass transition temperature of the hydrophobic polymer. Accordingly, with liquisolid compacts the coalescence of the polymer particles occurs at lower temperatures than with conventional matrix tablets. This more pronounced coalescence of polymer particles of liquisolid compacts leads to a matrix with lower porosity and higher tortuousity. Consequently, the drug is surrounded by a fine network of the hydrophobic polymer resulting in a sustained release of the drug [Karmarkar *et al*., 2010a].

Moreover, it has been shown that the addition of HPMC increases the retardation effect of liquisolid compacts. HPMC is commonly used for the preparation of hydrophilic matrix systems. Depending on the molecular weight it will either swell in contact with water forming a hydrated matrix layer through which the drug has to diffuse or erode resulting in zero order drug release kinetics [Nokhodchi *et al*., 2007; Nokhodchi *et al*., 2010].

If the *R*-value (the ratio of carrier to coating material) is low, which means that the applied amount of silica (the coating material) is high, oversaturation might occur resulting in local precipitation of the drug and thus, decreased release rates. Moreover, the higher the percentages of undissolved drug in the liquid formulation the slower the release rate. This is especially important for poorly soluble drugs, as the dissolution rate of these drugs is low [Spireas and Bolton *et al*., 1998].

1.1.5 Method of preparation of liquisolid system

A liquid lipophilic drug or a solid water-insoluble drug can be converted into a liquisolid system without being further modified. Solid water-insoluble drugs should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration [Nokhodchi *et al*., 2011]. Next, a

certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as powder and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers [Spireas, 1998; Spireas and Sadu, 1998; Spireas *et al*., 1998].

The resulting wet mixture is then converted into a dry-looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Excipients possessing fine and highly adsorptive particles, such as various types of amorphous silicon dioxide (silica), are most suitable for this step. [Chen *et al*., 2012] Before compression or encapsulation, various adjuvants such as lubricants and disintegrants (for immediate release) or binders (sustained-release) may be mixed with the finished liquisolid systems to produce liquisolid compacts i.e. tablets or capsules [Spireas *et al*., 1999].

Determining the required amount of excipients

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. Calculating the required amounts of powder excipients (carrier and coating materials) is critical in the formulation of the compacts. A mathematical approach for the formulation of liquisolid systems has been developed by Spireas, (1998). The approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination [Nagabandi *et al*., 2011].

Flowable liquid retention potential (Φ) which is also called holding capacity of sorbent is the maximum weight of liquid that can be retained per unit weight of powder material in order to produce an acceptably flowing liquid/powder admixture. Exceeding the Φ value causes saturation of the interior of the particles, resulting in the formation of a liquid layer on the carrier particles' available surface [Gavali *et al*., 2011].

The liquisolid flowability test (LSF) is employed to determine the flowable liquid retention potential (Φ-value) of several powder excipients likely to be included in liquisolid compacts. The test is basically a titration-like procedure in which 25 to 30

grams of mixtures of the powders under investigation, with increasing amounts of a non-volatile solvent (i.e., liquid/solid weight composition), such as, polyethylene glycol are prepared using a standard mixing process which ensures uniformity, and their flow rate and consistency are assessed using a recording powder flow meter [Hentzschel *et al*., 2011a]. The liquid/solid weight composition (w/w) in that admixture, which just complies with a desired and preselected limit of acceptable flowability, is taken as the Φ-value of the excipient. The non-volatile solvent used in the LSF test should be the one selected to be included in the liquid medication (drug solution or drug suspension) of the targeted liquisolid product [Spireas and Sadu, 1998; Spireas *et al*., 1998;].

The compressible liquid retention potential (ψ value) is the maximum weight of liquid that can be retained per unit weight of the powder material to produce an acceptably compressible powder admixture. In fact, this is the weight of liquid that can yield tablets of satisfactory mechanical strength without presenting any liquid squeezing out of liquisolid mass during compression [Gubbi and Jarag, 2010].

Generally, according to Spireas *et al* (1999); the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier:coating ratio of the powder system used which is represented by equation 1.1 as:-

$$R = Q/q \qquad \text{Eq. 1.1}$$

Where, R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation.

An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (Wl) to the weight of the carrier powder (Q) in the system.

$$Lf = W/Q \qquad \text{Eq. 1.2}$$

The powder excipients ratios R and liquid load factors Lf of the formulations are related as follows:

$$Lf = \Phi + \Phi c\ (1/R) \qquad \text{Eq. 1.3}$$

In order to calculate the required ingredient quantities, the Φ-values of powder excipients are utilized (Table 1.1). Therefore first, using Eq. 1.3, having the constants Φ (flowable liquid retention potential of the carrier) and Φc (flowable liquid retention potential of the coating agent) and that of the desired R value, Lf is calculated from the linear relationship of Lf versus 1/R. Next, based on liquid vehicle concentration, different weights of the liquid drug solution are used. So, by knowing both Lf and Wl, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (Wl) into an acceptably flowing and compressible liquisolid system could be calculated from equations 1.1 and 1.2 [Spireas *et al*., 1999; Spireas *et al*., 1998].

The method has been successfully applied to various water insoluble drugs to enhance their dissolution such as Bromhexine HCl [Gubbi *et al*., 2009], Carbamazepine [Tayel *et al*., 2008], Famotidine [Fahmy *et al*., 2008], Furosemide [Akinlade *et al*., 2010], Griseofulvin [Hentzschel *et al*., 2011b], Hydrocortisone [Spireas *et al*., 1998] Hydrochlorothiazide [Khaled *et al*., 2001], Indomethacin [Saeedi et al., 2011], Naproxen [Tiong *et al*., 2009], Piroxicam [Javadzadeh *et al*., 2005], Simvastatin [Burra *et al*., 2011], Repaglinide [El-Houssieny *et al*., 2010] etc. It has also been confirmed that, the method could be successfully be optimized to sustain the release of the drug such as Propranol [Javadzadeh *et al*., 2008], Tramadol [Karmarkar *et al*., 2010] and Lornoxicam [Ganesh *et al*., 2011].

Table 1.1: Examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles.

	Flowable liquid retention potential (φ)		Compressible liquid retention potential (ψ)	
Powder excipients Systems	Propylene glycol	Polyethylene glycol 400	Propylene glycol	Polyethylene glycol 400
Avicel®PH102	0.16	0.005	0.224	0.242
Avicel®PH200	0.26	0.02	0.209	0.232
Cab-O-Sil M5(silica)with Avicel PH102	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (Silica)with Avicel PH200,	2.57	2.44	0.712	0.717

1.2 Diclofenac sodium

1.2.1 General Description, Pharmacodynamics and Pharmacokinetics

Diclofenac sodium (DS) is a potent NSAID of the phenylacetic acid class, ({2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid) which has analgesic, antipyretic and anti-inflammatory properties. It is mainly indicated in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It acts by irreversibly inhibiting the cyclooxygenase pathway of prostaglandin synthesis, which is the most common mediator of pain, inflammation and pyrexia [Mestorino *et al*., 2007].

Diclofenac Sodium, as anti-inflammatory agent, is twice as potent as indomethacin and 450 times as potent as aspirin. As an analgesic, it is six times more potent than indomethacin and 40 times more potent than aspirin in the phenyl-benzoquinone induced writhing assay in mice. As an anti-pyretic it is twice as potent as indomethacin and over 350 times as potent as aspirin in yeast induced fever assay in rats [Ahmad *et al*., 2010].

The active ingredient is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is a weak acid (pKa, 4.0) with a partition coefficient of 13 in octanol/phosphate buffer (pH 7.4). Under physiological conditions the solubility ranges from 17.8 mg/L in water at neutral PH to less than 1 mg/L at acidic PH [Khazaeinia and Jamali *et al*., 2003]. The structure of the diclofenac sodium is shown in Fig. 1.2.

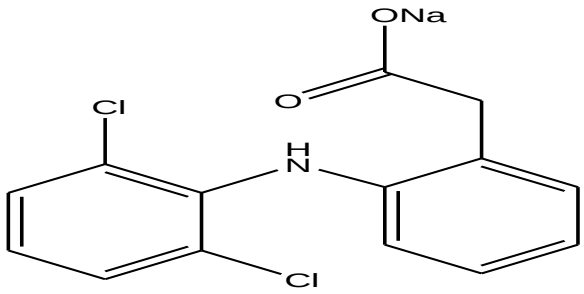

Figure 1.2: Structure of Diclofenac Sodium

The presence of the heteroatom's like nitrogen, oxygen, chlorine and sodium in the molecular structure of the drug causes high polarizability of the molecule and hence specific interactions with solvents that strongly affect the solubility in different solvents. Because of the presence of the -NH group that can act either as proton donor or proton acceptor toward the solvents and the presence of the carboxylic group, the drug possesses a lewis acid-base character [Manjunatha *et al*., 2007; Nayak, 2010].

When diclofenac sodium delayed-release tablets are administered orally after fasting, diclofenac is completely absorbed from the gastrointestinal tract. Of this, only 50% of the absorbed dose is systemically available [Magosso *et al*., 2004]. The biological half-life of the drug is aprox.120 min, therefore it requires multiple dosing. It is also extensively bound to plasma proteins (99%) and is metabolized in the liver; its metabolites being mainly excreted in urine (approx. 65%) [Ahmad *et al*., 2010; Hasan *et al*., 2005]. This drug is very interesting in modified release oral dosage forms, especially due to its relative short biological half-life, the hazards of adverse gastro-intestinal reactions and chronic nature of treatment [Kincl *et al*., 2004].

1.2.2 Solubility of Diclofenac Sodium

Among common NSAID, diclofenac sodium is one of the least soluble compounds even though presented as sodium and potassium salt [Oberli *et al*., 1994]. The drug is poorly soluble in a dissolution media with pH values more than 1 unit below the pKa in which the active ingredient present mostly in its free acid form, which is even less soluble than the salt. Consequently, the solubility of the active ingredient in the dissolution medium with pH less than 3 is very low (0.003 g/L in simulated gastric fluid). [Jain *et al*., 2009; Nayak 2010; Llinas *et al*., 2006].

As the pH value increases, the solubility of the drug increases (13 g/L in simulated intestinal fluid) due to the contribution from the ionized form until the highest solubility of the ionized form is reached in phosphate buffer solution pH 8.0 suggesting the composition, pH and ionic strength affects the solubility and absorption of the drug In conclusion, solubility of diclofenac sodium is higher in dissolution media with lower ionic strengths and higher pH. [Gupta and Sehrawat, 2011; Žilnik *et al*., 2007]

1.3 Present Study

At present 40% of the drugs in the development pipelines, and approximately 60 % of the drugs coming directly from synthesis are poorly soluble. The problem has been the major challenging issue for the industry especially during the development of ideal solid dosage form unit [Yadav *et al*., 2009a]. Release enhancement of poorly soluble drug has been attempted using different mechanisms but unfortunately, most of them are associated with limitations [Hentzschel *et al.,* 2011b]. Therefore, introduction of new methods such as liquisolid compact technology is critical for the development of new drugs.

Liquisolid compact technology has several important features such as low cost formulations, similar production process as that of conventional tablets, omits the process approaches such as micronization techniques, possibility of modified release preparations using suitable formulation ingredients, large scale industrial production and compared with other formulations such as solid dispersions minimized excipients usage [Lakshimi *et al*., 2012].

In this study the method, LSC has been used to enhance or sustain the release of diclofenac sodium. This active ingredient is chosen for three reasons. The first reason

being the most commonly prescribed analgesic and antipyretic drug in our country as well as worldwide. The other one is the poor solubility of the drug which imparts a great deal of problem in industrial production of the drug. The active ingredient exists in acidic form in acidic solutions such as gastric juice, and is practically insoluble in water but soluble in intestinal fluid. The third reason is the adverse effect of the medication on frequent administration such as gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding which lead to poor patient compliance [Iqbal *et al*., 2010]. Therefore, it is believed that the drug is the best candidate to evaluate the liquisolid technology as to enhance or sustain the release.

2. OBJECTIVES

2.1 General objective

- To enhance the dissolution of diclofenac sodium and sustain its release from liquisolid compact

2.2 Specific objectives

- To enhance the dissolution of diclofenac sodium using liquisolid technology,
- To sustain the release of diclofenac sodium using liquisolid technology,
- To study the effect of the non-volatile solvents on the release of the drug from the compact,
- To study the effect of the ratio of the amount of carrier to the amount of coating material on the release of the drug, and
- To study the effect of the concentration of the drug on the release profile of the drug from the compact,

3. MATERIALS AND METHODS

3.1 Materials

Colloidal silica (Aerosil® 200) (Evonik Industries AG, Essen, North Rhine-Westphalia, Germany), diclofenac sodium; diclofenac sodium reference standard (China Associate Co. LTD, East Shenzhen,China), and Propylene glycol BP/USP (Horst G.F von Valtier GmbH and Co .LTD, Glinde, Germany) were generous gifts from the Ethiopia Pharmaceutical Manufacturing Share Company. Eudragit® RL, magnesium stearate, microcrystalline cellulose (Avicel® PH101 and Avicel® PH200), PEG 400, Phosphate buffer, Polysorbate 80 (Tween 80), Potato starch, Sodium Starch Glycolate (SSG), Voltarene® SR 75 mg (Novartis Farma S.P.A Torre Annunziata Italy for Novartis Pharma A.G Basle, Switzerland; Manu. Date 12/2012 Batch no T1251 Exp. Date 11/2015) and Voltarene® 50 mg (Novartis Farma S.P.A Torre Annunziata, Italy for Novartis Pharma A.G Basle Switzerland; Manu. Date 08/2012 Batch no T0808 Exp. Date 07/2017) were used as received.

3.2 Methods

3.2.1 Solubility studies

The solubility of diclofenac sodium was determined in various solvents (phosphate buffer (pH 6.8), 0.1N hydrochloric acid, Tween 80, PG, and PEG 400). Saturated solutions prepared in the vehicles were kept in a shaker (Stuart® Miniorbital shaker, Stone, Staeeord shire ST15 OSA, UK) for 48 hr at 25˚C. The solutions were then filtered and their concentration was determined by UV-spectrophotometer at 276 nm.

3.2.2 UV calibration curve of diclofenac sodium in 0.1N Hydrochloric Acid

Stock solution of DS reference standard was prepared by transferring 68 mg of DS reference standard into a 100 ml volumetric flask containing 10 ml of 0.1N sodium hydroxide and diluting with water to volume. From this stock solution, six different concentration (6.8, 10.2, 13.6, 17, 20.4 and 23.8 µg/ml) of the solution were transferred to 100 ml volumetric flasks and diluted with a mixture of 0.1N hydrochloric acid and 5N sodium hydroxide (90:2) to volume. The UV absorbance readings of these solutions were

measured at 276 nm using UV/Visible spectrophotometer (CECIL CE 1021, England). A mixture of 0.1N hydrochloric acid and 5N sodium hydroxide (90:2) was used as a blank (USP, 2007). Then, the absorbance versus concentration of solutions were plotted to obtain the calibration curve. The Beer Lambert calibration curve (Figure 3.1) yielded a linear regression equation of A= 0.0306C-0.00368 (where A is the absorbance and C is the concentration in µg/ml with 95% confidence interval) and coefficient of determination (R^2) of 0.99931.

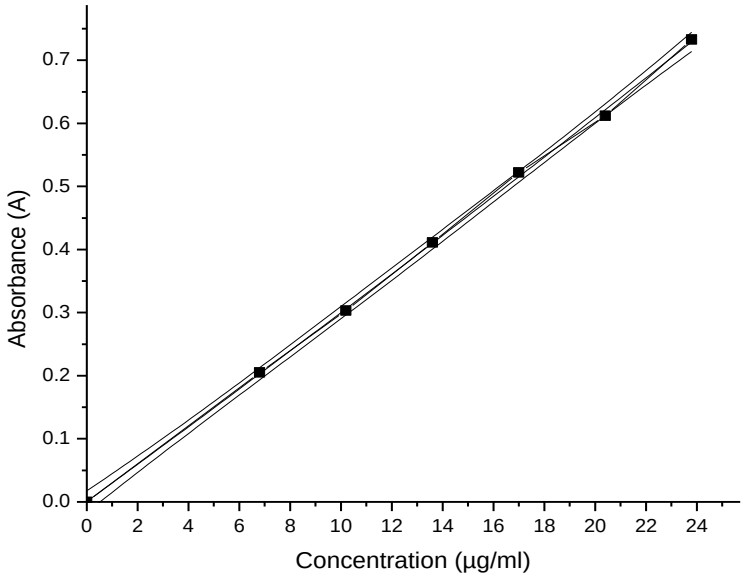

Figure 3.1: UV absorption calibration curve of diclofenac sodium reference standard in 0.1N HCl at 276 nm with 95% confidence interval

3.2.3 UV calibration curve of diclofenac sodium in phosphate buffer (pH 6.8)

Stock solution containing 100 µg/ml of DS reference standard in phosphate buffer of pH 6.8 was prepared. From this stock solution, eight different concentrations (7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25 µg/ml) were prepared. The UV absorbance reading of the solution was measured at 276 nm using UV/Visible spectrophotometer (CECIL CE 1021, England). Phosphate buffer (pH = 6.8) was used as a blank. Then, the absorbance versus concentration of the solution was plotted to obtain the calibration curve. The Beer's Lambert calibration curve (Figure 3.2) yielded a linear regression equation of A=

0.02797C-0.00504 (where A is the absorbance and C is the concentration in µg/ml with 95% confidence interval) and R^2 of 0.99918.

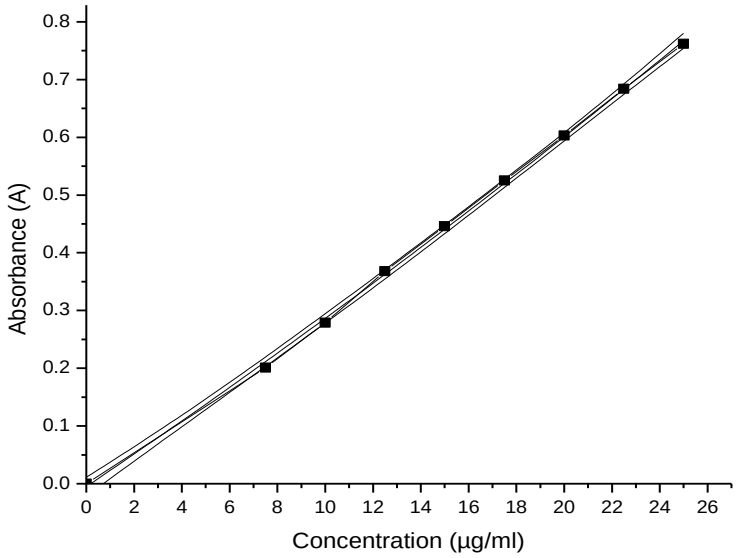

Figure 3.2: UV absorption calibration curve of diclofenac sodium reference standard in phosphate buffer (pH = 6.8) at 276 nm with 95% confidence interval

3.2.4 Preparation of enhanced release liquisolid compact

The enhanced release liquisolid compact (ERLSC) preparation was carried out as described by Spireas and Sadu, (1998). A calculated quantity of DS was dissolved in non-volatile solvent of interest (PEG 400 or PG) to 80 °c over a water bath. The resulting hot medication was then incorporated in to the specified quantities of carriers (Avicel® PH101 or Avicel® PH200) and coating materials (Aerosil® 200) determined according to liquid retention potential of the these excipients in the respective solvent (Section 1.1.5.1) and different formulations of ERLSC were prepared accordingly (Table 3.1-Table 3.5).

Mixing process was carried out in three steps. In the first stage, the system was blended at an approximate mixing rate of one rotation per second for one minute in order to evenly distribute liquid medication in the carrier. In the second stage, the liquid/ carrier admixture was evenly spread as a uniform layer on the surfaces of a mortar and left standing for 10 min to allow drug solution to be absorbed by interior of powder particles.

Then the coating material was incorporated to convert the wet surface to dry one by using the same procedure as that of first stage. In the third stage, the powder was scraped off the mortar surfaces by means of spatula and then blended with the disintegrant for another 5 min in a Turbula mixer (Willy A. Bachofen AG. Turbula 2TF Basel Switzerland). This gave the final liquisolid formulation ready to be compressed [Kulkarni *et al*., 2010].

According to Spireas *et al*. (1998), flowable liquid retention potential of Avicel®101 and Aerosil®200 in PG are 0.15 and 3.31, respectively, and flowable liquid retention potential of Avicel®200 and Aerosil®200 are 0.26 and 2.57, respectively. In PEG 400, flowable liquid retention potential of Avicel®101 and Aerosil®200 are 0.16 and 3.20, respectively. In all formulations Aerosil®200 was used as a coating agent. To study the release property, the prepared ERLSC was then compared with Voltarene® 50mg.

Table 3.1: Composition of Formulation 1 containing DS concentration in the liquid vehicle (PG) (% w/w) using Avicel® PH101 as a carrier

Formulation code	%w/w	R value	Wl (mg)	Lf	Q (mg)	q (mg)	SSG (mg)	1TW (mg)
F11	52	10	95.6	0.48	199.17	19.92	15.74	330.43
F12		20		0.32	298.75	14.93	20.46	429.74
F13		30		0.26	367.69	12.26	23.78	499.33
F14	60	10	83.3	0.48	173.54	17.35	13.71	287.90
F15		20		0.32	260.31	13.01	17.83	374.45
F16		30		0.26	320.38	10.67	20.72	435.07
F17	70	10	70.8	0.48	147.50	14.75	10.18	243.23
F18		20		0.32	221.25	11.06	15.15	318.26
F19		30		0.26	272.31	9.08	17.61	369.80

N.B. 1TW (One tablet weight), Wl (weight of the liquid medication), Q (amount of the carrier) and q (amount of the coating agent) and using aerosil® 200 as coating agent and SSG as a disintegrant

Table 3.2: Composition of Formulation 2 containing diclofenac sodium concentration in the liquid vehicle (PG) (% w/w) using Avicel® PH200 as a carrier

Formulation code	%w/w	R value	Wl (mg)	Lf	Q(mg)	q (mg)	SSG (mg)	1TW (mg)
F21	52	20	95.6	0.39	245.13	12.26	17.65	370.64
F22	70	20	70.8	0.39	181.54	9.08	13.07	274.49

N.B. 1TW (One tablet weight), Wl (weight of the liquid medication), Q (amount of the carrier) and q (amount of the coating agent) and using aerosil® 200 as coating agent and SSG as a disintegrant

Table 3.3: Composition of Formulation 3 containing diclofenac sodium concentration in the liquid vehicle (PEG 400) (% w/w) and Avicel® PH101 as a carrier

Formulation code	%w/w	R value	Wl (mg)	Lf	Q (mg)	q (mg)	SSG (mg)	1TW (mg)
F31	52	20	100	0.32	312.5	15.63	21.41	449.54
F32	70	20	72	0.32	225.00	11.25	15.41	323.66

N.B. 1TW (One tablet weight), Wl (weight of the liquid medication), Q (amount of the carrier) and q (amount of the coating agent) and using aerosil® 200 as coating agent and SSG as a disintegrant

Table 3.4: Composition of Formulation 4 containing diclofenac sodium concentration in the liquid vehicle (PG) (% w/w) using Avicel® PH101 as a carrier and PS (potato starch) as a disintegrant

Formulation code	%w/w	R value	Wl (mg)	Lf	Q (mg)	q (mg)	PS (mg)	1TW (mg)
F41	52	20	95.6	0.32	298.75	14.93	20.46	429.74
F42	70	20	70.8	0.32	221.25	11.06	15.15	318.26

N.B. 1TW (One tablet weight), Wl (weight of the liquid medication), Q (amount of the carrier) q (amount of the coating agent) and using aerosil® 200 as coating agent

Table 3.5: Composition of Formulation 5, Liquisolid compact of diclofenac sodium prepared without heating F51 (PG and Avicel® PH101) F52 (PG and Avicel® PH200) and F53 (PEG 400)

Formulation code	%w/w	R value	Wl (mg)	Lf	Q (mg)	q (mg)	SSG (mg)	1TW (mg)
F51	52	20	95.6	0.32	298.75	14.93	20.46	429.74
F52	52	20	95.6	0.39	245.13	12.26	17.65	370.64
F53	52	20	100	0.32	312.5	15.63	21.41	449.54

N.B. 1TW (One tablet weight), Wl (weight of the liquid medication), Q (amount of the carrier) q (amount of the coating agent) and using aerosil® 200 as coating agent and SSG as a disintegrant

3.2.5 Preparation of sustained release liquisolid compact

Sustained release liquisolid compacts (SRLSC) were prepared as described by Spireas and Bolton (1998). A quantity of DS was dissolved in non-volatile solvent of interest (Tween 80 or PG) to 80 °c over a water bath. The resulting hot medication was then incorporated into the quantities of carrier (Avicel®101 or Eudragit®RL) and then coating materials (Aerosil® 200) determined according to liquid retention potential of these excipients in the respective solvents (Section 1.1.5.1) and different formulations of

sustained release liquisolid compact (Table 3.6) were prepared accordingly. 70% liquid medication (solvent + drug) and R value of 20 were used to prepare the liquisolid compacts [Hentzschel, 2011; Nokhodchi *et al.*, 2010]. The mixing process of the liquisolid compacts were carried out in three steps as described earlier (section 3.2.4). The SRLSC prepared was then compared with marketed sustained release diclofenac sodium (Voltarene® SR 75 mg)

Table 3.6: Composition of various sustained Release formulation of Diclofenac Sodium Liquisolid Compact (Formulation FS)

Formulation code	DS (mg)	Lf	Aerosil® 200	Wl	Avicel ® 101	Eudragit ® RL	1TW (mg)
FS1	75	0.28	18.34	102.7		366.78	488
FS2	75	0.40	12.84	102.7	256.75		372
FS3	75	0.35	14.67	102.7		293.42	411

N.B. PG (FS1) and Tween 80 (FS2 and FS3)

3.2.6 Flow properties of the liquisolid system

3.2.6.1 Hausner's Ratio (HR) and Carr's Index (CI)

For each formulation of both ERLSC and SRLSC, samples of 20 g of liquisolid powder were carefully introduced into a 250 ml graduated glass cylinder and the volume was noted. The bulk density (D_b) of each formulation was then obtained by dividing the weight of samples by their respective volumes. Bulk density recorded is an average of three determinations. Then, the liquisolid powder was tapped 500 times using tapped densitometer (ERWEKA, SVM 20, Germany). The volume was noted after tapping. The tapped density (D_t) of each formulation was then obtained by dividing the weight of sample by the final tapped volume of the sample contained in the cylinder Tapped density recorded is an average of three determinations. Then, the HR and CI of each formulation were calculated from bulk and tapped densities using Equation 3.1 and Equation 3.2, respectively.

$$Housner's\ Ratio = \frac{Db}{Dt}$$ Eq.3.1

$$Carr's\ index = \frac{Dt-Db}{Dt} \times 100$$ Eq.3.2

3.2.6.2 Angle of repose

Measurement of angle of repose was performed by using a fixed funnel method. Accordingly, 20 g of the sample was allowed to flow through a glass funnel orifice with an inner diameter of 15 mm from a height of 10 cm. The angle of repose (θ, degree) was calculated by substituting the values of the base radius 'R' and pile height 'H' in Equation 3.3.

$$Angle\,of\ repose\ (\theta) = \tan^{-1}\left(\frac{H}{R}\right)$$ Eq. 3.3

3.2.7 Post compression studies

The powders prepared using liquisolid technology were compressed with an eccentric tablet press (Korsch EKO,7891Berlin,Germany) using flat faced punches and a die of 10mm diameter. In case of ERLSC the tablet hardness was fixed accordingly from 45-70 N and for SRLSC from 130-150N.

3.2.7.1 Hardness test

The hardness of formulated liquisolid tablets, 24 hr after tableting, were assessed using a hardness tester (Schleuniger, 2E/205, Switzerland) and the mean hardness determined by recording the crushing strength in Newton.

3.2.7.2 Friability test

A sample of ten tablets were accurately weighed and placed in the drum of the Friability tester (ERWEKA, TAR 20, GERMANY) and allowed to rotate at 25 rpm for 4 min. The tablets were then removed, dedusted and accurately weighed. The percentage loss in weight with respect to the initial value was used as a measure of friability.

3.2.7.3 Drug content of formulated tablets

Ten tablets from each formulation were randomly chosen and weighed. An amount equivalent to 50 mg of diclofenac sodium was then extracted using 200 ml methanol and filtered. Then 0.5 ml of this solution was diluted to 100 ml with methanol. The average absorbance readings of resultants solutions were taken with a UV spectrophotometer.

3.2.7.4 Weight variation

The average weights of 20 tablets along with standard deviation of entire formulations were taken and the percentage of weight variation of individual tablets from the average weight was calculated and compared with USP weight variation test.

3.2.7.5 Disintegration time

The disintegration time of SRLSC and ERLSC was determined according to USP/NF specification (USP XXX/NF XXV, 2007), by placing six tablets in disintegration tester (CALEVA G.B. Caleva LTD., UK) filled with distilled water and maintained at 37 ± 2 °C. The tablets were considered to completely disintegrate when all the particles passed through the size 10 mesh screen of the basket rack assembly and if any residue remains, it must have a soft mass with no palpably firm core.

3.2.8 *In vitro* dissolution studies of Enhanced Release Liquisolid Compact

The *in vitro* dissolution study was carried out using USP Type II dissolution apparatus (paddle Apparatus) (USP30/NF25<711>, 2007), and the test was performed on six tablets from each formulation complying friability and crushing strength tests. The study was carried out in 900 ml of 0.1N hydrochloric acid (pH 1.2) for 1hrs. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37+0.5 ^{o}C and 50 rpm paddle rotation. An aliquot of 5 ml was withdrawn at 5, 10, 20, 40 and 60 min replacing 5 ml of fresh corresponding medium into the dissolution flask to maintain sink condition. The sample was then filtered through Whatman No. 1 filter paper and the absorbance readings were taken with UV/Visible Spectrophotometer (CECIL, CE 1021, England) at 276 nm after appropriate dilution with respective blank solution.

3.2.9 *In vitro* dissolution studies of Sustained Release Liquisolid Compact

In the *in vitro* dissolution studies of sustained release liquisolid compacts the same procedure was followed as those of ERLSC (section 3.2.8) except that the studies were carried out in 900 ml of 0.1N hydrochloric acid (pH 1.2) for the first 2 hrs and then changed to 900 ml of phosphate buffer (pH 6.8) for the next 10 hr and an aliquot of 5ml was withdrawn at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hr replacing 5 ml of fresh corresponding medium into the dissolution flask to maintain sink condition

3.2.10 Drug release kinetics and mechanism of drug release

Data obtained from *in vitro* release studies were fitted into various kinetic models. The kinetic models used were zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model (Equation 3.5 through Equation 3.9).

Zero order release kinetics model

$$Q = Q_o - Kt \qquad \text{Eq.3.5}$$

Where, Q is the amount of drug remaining in the dosage form at time t, Q_o is the quantity of drug present initially in the dosage form and K is the zero order release constant.

First order release kinetics model

$$\ln Q = \ln Q_o - Kt \qquad \text{Eq.3.6}$$

Where, Q is the amount of drug remaining in the dosage form at time t, Q_o is the quantity of drug present initially in the dosage form, and K is the first order release constant.

Higuchi square root kinetics model

$$\frac{M_t}{M_\infty} = Kt^{1/2} \qquad \text{Eq.3.7}$$

Where, M_t/M_∞ is the fraction release of drug at time t, and K is rate constant.

Hixson-Crowell cube root kinetics model

$$Q^{1/3} = Q_0^{1/3} - Kt \qquad \text{Eq. 3.8}$$

Where Q is the amount of drug remaining in the dosage form at time t, Q_o is the quantity of drug present initially in the dosage form and K is the rate constant for Hixson-Crowell rate equation.

In order to find out the mechanism of drug release from the compact, drug release data were fitted to the Korsmeyer-Peppas model (Equation 3.9):

$$\frac{M_t}{M_\infty} = Kt^n \qquad \text{Eq. 3.9}$$

Where $M_t/M_\infty$is the fraction of drug released at time t, K is the rate constant and n is the release exponent that is used to characterize different release mechanisms [Dash *et al*., 2010].

3.2.11 Evaluation of the formulations using model-independent approach

According to US FDA guidance for dissolution data equivalence, a model-independent approach is recommended. This involves use of the similarity factor (f2), which provides a simple means of comparing data. US FDA guidance proposes that f2 values of 50-100 indicate equivalence in dissolution profiles. This value is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. [Karmarkar *et al*., 2010]

$$f2 = 50 \times \log \{[1 + (1/n) \Sigma^n t_{=1} (R_t - T_t)^2]^{-0.5} \times 100\} \qquad \text{Eq. 3.10}$$

Where *n* is the number of time points, R is the dissolution value of the reference at time t, and T is the dissolution value of the test at time t.

3.2.12 Statistical analysis

To compare individual differences in physicochemical and tablet properties the data was analyzed using Analysis of Variance (ANOVA) on Origin 8.5 (OriginLabTM Corporation, USA) statistical software. At 95% confidence interval, p-values of ≤ 0.05 were considered statistically significant. All the data measured and reported are averages

of a minimum of triplicate measurements and the values are expressed as mean ± standard deviation.

4. RESULTS AND DISCUSSION

4.1 Solubility of diclofenac sodium in various solvents

The solubility results in Table 4.1 show that sodium salt of diclofenac has lower solubility in acidic environment but much higher solubility in phosphate buffer. It was also observed that diclofenac sodium has much better solubility in the non-volatile solvent PG than PEG 400 and Polysorbate (Tween 80). Therefore, PG was used as a solvent of choice for the enhanced release formulation and PEG 400 for comparison purpose. Based on the results of solubility studies, Tween 80 was the solvent of choice for sustained release formulation.

Table 4.1: Solubility of diclofenac sodium in different solvents

Solvent	Phosphate buffer(pH6.8) ±SD	HCl (pH1.2) ±SD	PG ±SD	PEG400 ±SD	Tween 80 ±SD
Solubility (g/100g)	0.035 ± 1.65	1×10^{-4}± 2.04	9.64 ±1.89	8.89 ± 2.34	0.71± 2.59

4.2 Preliminary studies

Liquisolid preparations may exhibit poor and erratic flow and compaction properties. As the method is based on converting a liquid medication (a liquid drug or solution of a drug in nonvolatile solvent) to flowable and compressible powder, flowability of liquisolid system is the governing property. In the preparation of LSC with preferred features various experimental condition were checked. The concentration of the liquid medication and the ratio of powder substrates are the major factors determining these features of the compact.

R value ranging from 5 to 40 and concentrations of the liquid medication ranging from 20% to 70% were prepared in an attempt to choose the right formulation. This was done using PG as the solvent and Avicel® PH101 and Aerosil® 200 as carrier and coating

agents, respectively, and using flowable liquid retention values of the additives in the solvent used [Nokhodchi *et al*., 2011].

From the experiments it was found that the R value affects the flowability ($P < 0.05$) as well as the tablet property of the compact. As small value of R is used a sticky powder of flowability which did not comply with the US Pharmacopeia limit ($HR \leq 1.25$) was seen, which could have resulted due to the less amount of the carrier used. A higher R value was associated with very high tablet weight and was found to be hard to compress [Veen *et al*., 2005]. From this study, it was also determined that tablets hardness of 45 N -70 N for ERLSCs and 130-150 N for SRLSCs provide appropriate tablet property.

The other factor is concentration of the medication, the least concentrated formulation need a higher amount of the carrier to attain flowable and compressible powder system which also lead to high tablet weight. The R value and the concentration were also found to influence the drying time of the powder formulated. The less concentrated preparation takes longer ($\geq$ 25 min) to dry but when Aerosil®200 was used in larger quantity the drying time was improved ($\leq$ 15 min).

Based on the findings of this preliminary study, 10, 20 and 30; R values and 52%, 60% and 70% as concentration of medication were chosen for subsequent study.

4.3 Enhanced release liquisolid compact of diclofenac sodium

4.3.1 Powder property of enhanced release liquisolid compact

As the technology liquisolid compact is based on converting a liquid formulation into flowable and compressible powder, the flowability of liquisolid compacts is the major factor to be evaluated. The non-volatile solvent used; the concentration of the liquid medication as well as the ratio of the carrier and coating material being the major factors. In addition, in this experiment it was also observed that the type of the carrier showed a difference in the value of the flowability indicators.

All the formulations were prepared according to flowable and compressible liquid retention potentials of the carriers and the coating material used. The flow of all formulation were found to lie within acceptable range of HR (below and between 1.25

and 1.5), CI (below and between15 and 40) and angle of repose (below and between 30 and 40) confirming the proposed method of liquisolid compact preparation by Spireas (1998).

The results in Table 4.2 show that, the flow of the liquisolid powder is highly affected by flowable liquid retention potential of the Avicel® PH101 and Aerosil®200 in the respective solvent (PG) which mimic the amount of the excipients that will convert the liquid medication to powder. Three different concentrations (52, 60, 70) having different carriers to coating ratio (10, 20, 30) of this preparations were compared as to their flowability. There was statistically significant difference ($P < 0.05$) in flow property as concentration and R value were varied. F19 has better flow than F11 implying concentrated preparations have better flowability. It was also observed that as R value increases (F14 to F16) the flow of the liquisolid powder gets better because Lf value decreases and higher amount of carrier is used.

Table 4.2: Flow properties of Formulation 1 (PG and Avicel® PH101)

Flow	F^1_1	F^1_2	F^1_3	F^1_4	F^1_5	F^1_6	F^1_7	F^1_8	F^1_9
HR	1.29±0.10	1.28±0.16	1.27±0.18	1.23 ±0.11	1.21 ±0.11	1.19 ±0.19	1.17 ±0.10	1.15 ±0.14	1.14 ±0.05
CI	22.62± 0.20	21.92± 0.23	21.34± 0.23	19.23 ±0.14	17.30± 0.19	15.96 ±0.26	15.38 ±0.16	13.08 ±0.14	12.31 ±0.17
Θr	36.19± 0.41	36.91± 0.56	35.69± 0.23	34.12 ±0.21	30.54± 0.14	31.66 ±0.13	30.93 ±0.13	29.12± 0.13	28.40± 0.03

N.B. Mean± SD (n=3)

Usually bigger particles (Avicel® PH200 = 182.51 μm) show better flowability than smaller particles (Avicel® PH101 = 47.92 μm) but liquisolid formulations showed a reduction ($p < 0.05$) in flowability in comparison with pure carriers (Table 4.2 and 4.3). This could be due to the presence of viscous liquid medication (PG) on the surface of the carriers in liquisolid formulations. As the particle size of Avicel® PH200 is large, the carrier particles will have a low surface area which can accommodate a thicker layer of liquid medication distributed around its surface. Therefore, the liquid around these

particle surfaces will be thicker than if the particles were small. This will increase the tendency of particles to stick together, hence poor flowablity of powder. Furthermore, the added liquid could increase cohesive and adhesive forces between particles due to the wall effect. The result is in agreement with previous study [Javadzadeh *et al*., 2009].

Table 4.3: Flow properties of Formulation 2 (PG, Avicel® PH200), 3 (PEG 400) and 4 (PS as a disintegrant)

Flow	F21	F22	F31	F32	F41	F42
HR	1.32±0.05	1.18±0.03	1.26±0.08	1.13±0.37	1.28±0.16	1.16±0.14
CI	24.23±0.13	15.19±0.1	21.58±0.33	11.46±0.40	21.82±0.23	13.78±0.14
Θr	31.56±0.74	27.12±0.71	37.07±1.07	26.91±1.32	36.91±0.56	28.42±0.13

N.B. Mean ± SD (n=3)

F32 is free flowing than that of F17 even if it has the same R value and concentration of medication. Thus, the type of solvent determines the Lf value which will affect the flowability in this case PEG 400 (F32) showed better powder property than that of PG ($P < 0.05$). The above observation based on concentration of medication was valid here too; F31 was less flowable than F32.

4.3.2 Tablet properties of enhanced release liquisolid compact

The parameters used to investigate tablet property of the compacts are hardness, friability, weight variation and content uniformity. As can be seen in table 4.4, weight variations of the tablets lie within the acceptable range, which is 10% for tablets weighing ≤ 324 mg and 7.5% for tablets weighing 324-650 mg [Lakshmi *et al*., 2012]. Except F19 (90.21%), the content uniformity of the liquisolid compact were within the acceptable range of not less than 95% and not more than 105% of the labelled potency. The results obtained are in agreements with reports on liquisolid compact elsewhere [Nokhodchi *et al*., 2005; Javadzadeh *et al*., 2007c]

Table 4.4: Tablet properties of Formulation 1 (PG + Avicel® PH101)

Tablet properties	F11	F12	F14	F15	F17	F18
Hardness (N)	53±1.72	47±1.39	54±2.03	49±1.42	68±1.82	65±2.53
Friability (%)	0.63±0.45	0.75±0.32	0.62±0.81	0.74±0.79	0.51±0.39	0.55±0.52
Weight variation (mg)	330.4±3.34	430.74±2.23	290.33±5.86	377.61±5.93	243.23±2.43)	318.26±2.32
Content uniformity (%)	98.21	99.01	102.32	101.21	97.21	96.45

N.B. Mean ± SD (n=3)

Hardness and friability of the liquisolid compact were found to be significantly ($p < 0.05$) influenced by the concentration of the medication; the R value; the type of the solvent and the type of the carrier. The hardness and friability of F13 (friability of 1.13%) and F16 (friability of 1.08%) were not within the acceptable range, and therefore excluded from further experiment.

Table 4.5: Tablet properties of Formulation 2 (PG + Avicel® PH200), 3 (PEG 400) and 4 (PS as a disintegrant)

Tablet properties	F21	F22	F31	F32	F41	F42
Hardness(N)	66±1.34	70±1.23	46±2.31	66±2.0	46±1.29	61±1.98
Friability (%)	0.59±0.87	0.43±0.54	0.78±0.06	0.59±0.32	0.79±0.41	0.66±0.48
Weight variation (mg)	370.64±5.32	269.49±7.62	450.54±6.01	323.66±5.35	429.74±5.63	319.26±5.45
Content uniformity (%)	95.98	96.72	103.27	98.23	96.74	101.43

N.B. Mean ± SD (n=3)

The results also showed that the concentrated formulation had higher hardness value and lower friability value which is due to smaller amount of PG used. PG as non-volatile solvent can act as a binder in low concentration, but it can have a negative effect on mechanical properties of liquisolid compacts in higher concentrations. Excessive non-volatile solvent produces the capillary state of powder aggregation, and therefore the surface tension effect becomes less significant in bringing the particles together, hence poor bonding. Another possible explanation for a decrease in tensile strength is formation of multilayers of PG at the particle surfaces when high level of non-volatile solvent is used. These layers may disturb or reduce inter-molecular attraction forces and thereby reduce tablet strength. The results in this study were in agreement with the result reported by Javadzadeh *et al*., (2009).

As R value decreases the hardness also decreases due to the high amount of coating agent employed which is associated with less compressibility. Improved tablet property was observed in case of PG than PEG 400 which could be due to the higher amount of coating agent used in case of PEG 400 [Veen *et al*., 2005]. This is despite the fact that the same R

value and concentration of medication is used (F11 and F31). In case of carriers; tablets containing Avicel® PH200 showed better tablet property than that of Avicel® PH101 (F21 and F11). The differences in all cases were found to be statistically significant ($P < 0.05$).

4.3.3 Drug release profile of enhanced release liquisolid compact

Figure 4.1 show the dissolution profiles of liquisolid compact of Formulation 1 as compared to Voltarene® 50 mg. The liquisolid compact exhibited a more distinct ($P < 0.05$) *in vitro* release profile than the marketed diclofenac sodium preparation. The percentage drug release from liquisolid compact in the first ten minute is higher (> 65%) than that of Voltarene® 50 mg (< 30%).

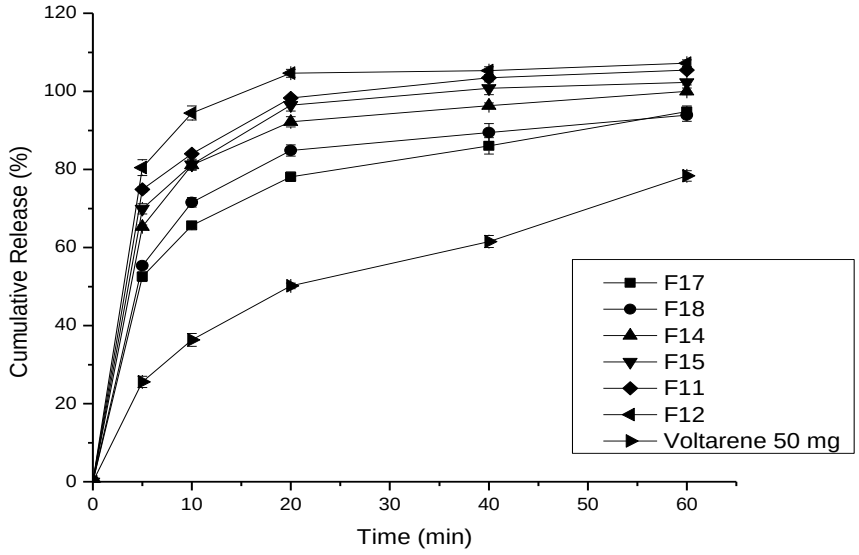

Figure 4.1: *In vitro* diclofenac sodium release profile from Formulation 1 and Voltarene® 50 mg (PG as a solvent, Avicel® PH101 as a carrier, a concentration of 52% (F11, F12), 60% (F14, F15) and 70% (F17, F18) using 10 and 20 as R values respectively)

Since the liquisolid compacts contain a solution of the drug in non-volatile vehicle used for preparation of the liquisolid compacts, the drug surface area available for dissolution is tremendously increased. In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state,

whereas the conventional preparations are merely exposed micronized drug particles [Javadzadeh *et al*., 2007b].

Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the conventional tablets. According to Noyes and Whitney, the drug dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer, but also to its surface area available for dissolution [Nokhodchi *et al*., 2011]. Moreover, since all dissolution tests for marketed and liquisolid diclofenac sodium preparations were carried out at a constant rotational paddle speed and identical dissolving media, it is assumed that the thickness of the stagnant diffusion layer and the diffusion coefficient of the drug molecules transported through it remain almost identical under each set of dissolution conditions [Yadav *et al*., 2009b]. Therefore the significantly increased surface area of the molecularly dispersed diclofenac sodium in the liquisolid compacts may be principally responsible for their observed higher dissolution rates.

As can be seen in Fig 4.2, the dissolution rates from the liquisolid compacts prepared with the two solvents (PG and PEG 400) were significantly different from each other ($P < 0.05$). That is liquisolids containing PEG 400 (F31 and F32) have relatively reduced dissolution rate than PG containing liquisolids (F12 and F18). This might be due to the lower solubility of the drug in PEG 400 compared to PG. As main attributes of enhanced dissolution from liquisolid compacts are higher surface area and increased wettability, the solubility of the drug in the non-volatile solvent is one of the major factors determining the release profile.

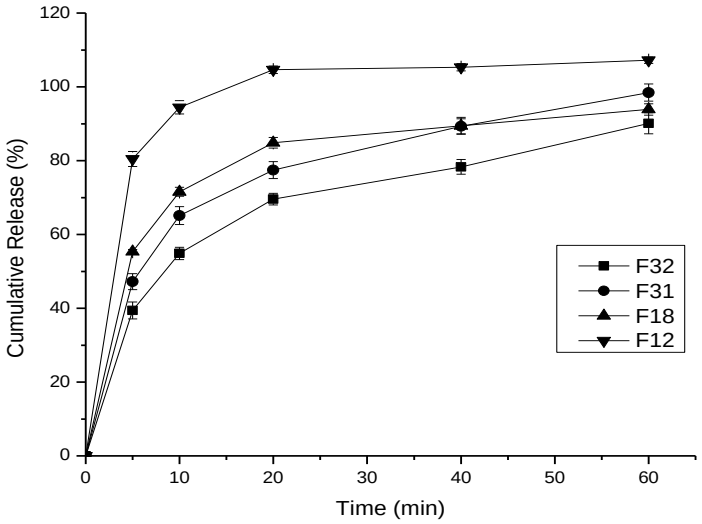

Figure 4.2: *In vitro* diclofenac sodium release profile from Formulation 3 depicting the effect of the solvent used (PG as a solvent for F12 (52%) and F18 (70%); PEG 400 as a solvent for F31 (50%) and F32 (70%) using Avicel® PH101 and R value of 20 for all Formulations)

In all formulations, as depicted in Fig. 4.3, the drug release is much higher when the concentration of the drug in the liquid medication is lower. This can also be explained by the amount of soluble form of the drug or molecular dispersion states of the drug in the formulations, which is directly proportional to the dissolution rate [Nokhodchi *et al*., 2005].

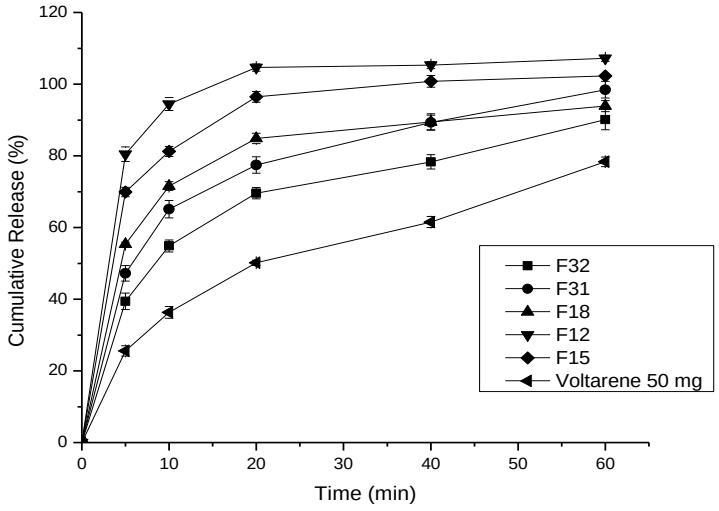

Figure 4.3: *In vitro* diclofenac sodium release profile showing the effect of concentration (PG as a solvent for F12 (52%), F15 (60%) and F18 (70%), PEG 400 as a solvent for F31 (50%) and F32 (70%) using Avicel® PH101 and R value of 20 for all Formulations)

Besides, as depicted in Fig. 4.4, the dissolution rate (µg/min) of liquisolid compacts increased with the decrease in concentration of the drug in the liquid medication. In a concentrated formulation, the amount of the drug in a molecularly dispersed state is less than those formulations containing smaller amount of DS. The amount of the drug in the soluble form can be determined from saturated solubility of DS in the solvents. Since, the saturation solubility of diclofenac sodium in PG is 9.64% w/w, about 46.2% of the DS is in soluble form in F12 formulation (this formulation contains 52% drug and 48% PG) whereas in F15 and F18 formulation, about 38.56% and 28.92% respectively of diclofenac sodium is as soluble form (F15 formulation contains 60% the drug and 40% PG and F18 contains 70% of the drug and 30% of PG). In the other formulations (F31 and F32) which contain the 52% and 70% concentrations of drug and PEG 400 as a solvent, about 44.45% and 26.67% of diclofenac sodium is in soluble form, respectively.

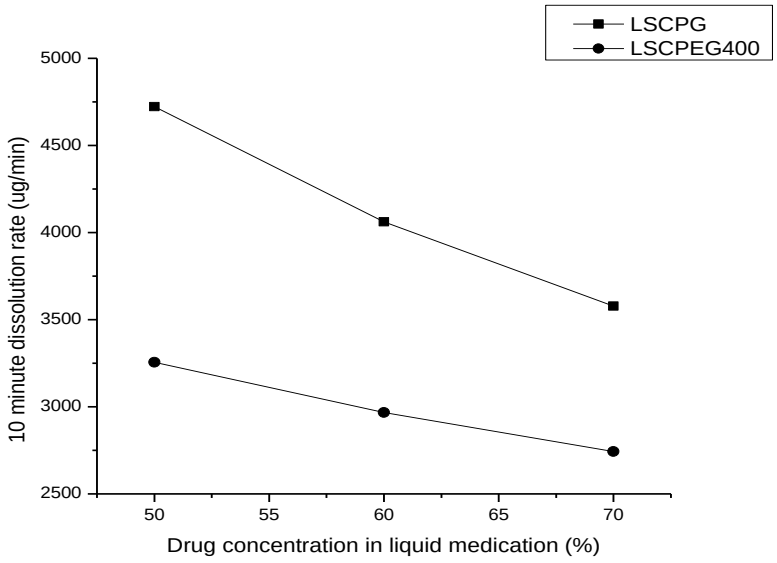

Figure 4.4: Ten minute dissolution rate of different diclofenac sodium concentration in liquisolid compacts in the solvents used (PG (LSC PG) and PEG400 (LSC PEG 400)).

In order to investigate the effect of fraction of the dissolved or molecularly dispersed diclofenac sodium (FM) of the prepared liquisolid tablets on the dissolution rates of the drug from liquisolid compacts, the FM was plotted against their corresponding dissolution rate (DR) values in ten minute (Fig 4.5). FM can be defined as the ratio of the diclofenac sodium saturation solubility in the liquid vehicle over the drug concentration in the liquid medication. In both solvents used in this study as shown in Figure 4.5, the DR in 10 min, increased in a linear manner, with increasing FM values of the liquisolid systems.

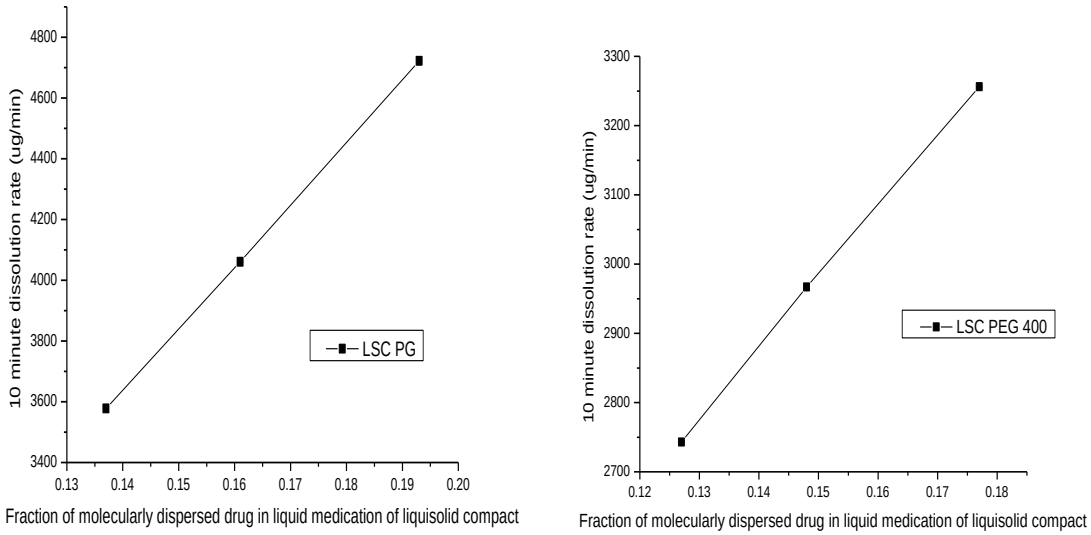

Figure 4.5: Fraction of molecularly dispersed drug in liquid medication of liquisolid compact in PG ($R^2$of 0.9999) and PEG 400 (R^2 of 0.9995)

Based on the results obtained, it also appears that dissolution is dependent on the microcrystalline cellulose particle size. As depicted in Figure 4.6, tablets containing Avicel® PH200 as a carrier showed lower dissolution rate in comparison to those containing Avicel® PH101. The particle sizes of the carriers Avicel® PH101 and Avicel® PH200 as determined by laser diffraction method were 74.92, and 182.51 µm, respectively [Javadzadeh *et al*., 2009]. As solution or suspension state of the drug was adsorbed on the surface of the carriers, it could be concluded that after disintegration of tablets, increased surface area to the medium fluid is available in F12 to F18 formulations. Thus, according to the Noyes–Whitney equation, higher dissolution rate is expected from these formulations [Hentzschel, 2011]

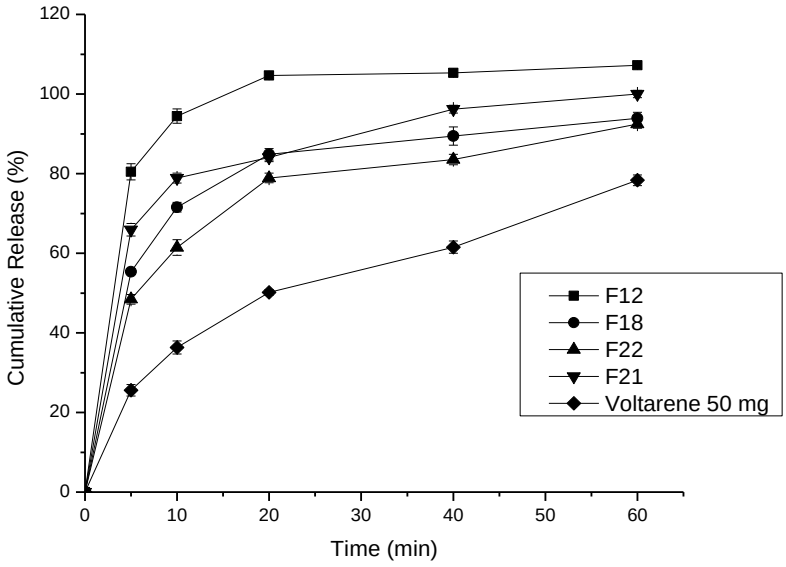

Figure 4.6: *In vitro* diclofenac sodium release profile from Formulation 1and Formulation 2 depicting the effect of the type of carriers (Avicel® PH101 as a carrier for F12 (52%) and F18 (70%), Avicel®PH200 as a carrier for F21 (52%) and F22 (70%) and for all Formulations PG is used as a solvent and R value of 20)

All of the tested tablets for the ERLSC formulations which have sodium starch glycolate as a disintegrant disintegrate in less than 45 sec. For those formulations having potato starch as a disintegrant it takes a little longer (1-3min). Because of the presence of a non-volatile solvent having a property of binding agent in the liquisolid formulation, delayed disintegration time is expected. However, in the liquisolid granules containing microcrystalline cellulose, a fast disintegration occurred which can be explained by the disintegrating property of microcrystalline cellulose. As has been depicted in Fig. 4.7, the drug released in the first ten min for those formulations containing potato starch as a disintegrant is less than those containing sodium starch glycolate ($P < 0.05$). But in the last min of drug release, the release from the two formulations was not significantly different (F18 and F42).

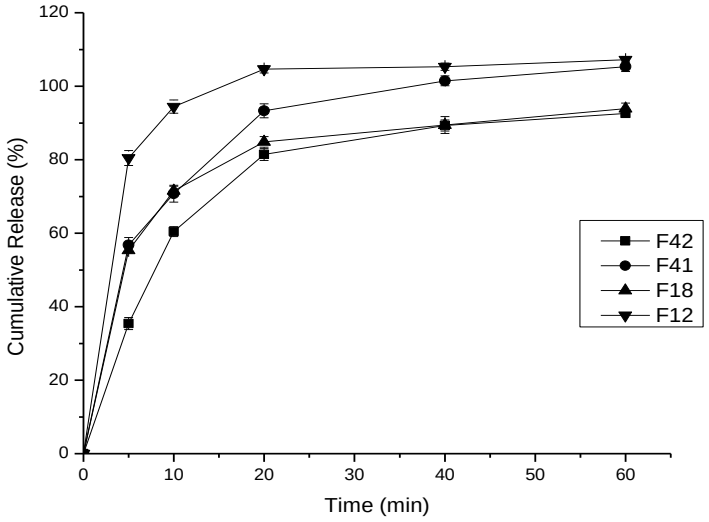

Figure 4.7: *In vitro* diclofenac sodium release profile from Formulation 4 depicting the effect of type of disintegrant (SSG (F12 and F18) and PS (F41 and F42)

The other major factor affecting *in vitro* drug release from liquisolid compact is the ratio of the carrier to coating material (Fig. 4.8). Liquisolid compacts with lower *R*-values contain relatively smaller amounts of carrier powder and larger quantities of fine drug loaded silica particles, and the ratios of the amounts of their liquid medication per powder substrate are relatively higher. On the other hand, liquisolid compacts with higher *R*-values contain low liquid/powder ratios, high presence of cellulose and low presence of silica.

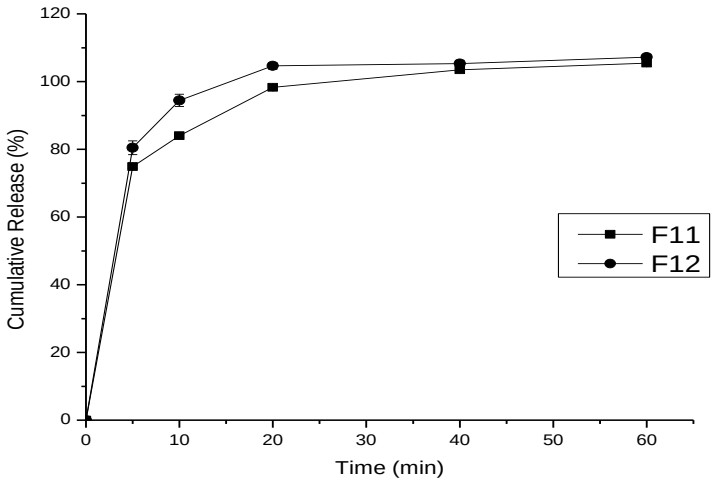

Figure 4.8: *In vitro* diclofenac sodium release profile depicting the effect of carrier to coating ratio (R value of 10 and 20 was compared for 52% formulations prepared by using PG as a solvent and Avicel® PH101 as a carrier.)

This could be directly associated with enhanced wicking, disintegration and deaggregation properties. Therefore, the liquisolid tablets with low *R*-values showed relatively poor dissolution [Aljaberi *et al*., 2009]. In addition, during the dissolution process, the primary particles produced after the disintegration of the liquisolid tablets with low *R*-values are overloaded with liquid medication. In such cases, even though the drug diffusion through the primary particles may be rapid, it might lead to overwhelming (solubility-wise) of the stagnant (adjacent to the primary particles) dissolution layers with drug, resulting in local precipitation of the drug during the initial stages of the dissolution process, thereby presenting decreased dissolution rates [Hentzschel *et al*., 2012].

During preparation of LSC, the temperature of the liquid medication was made in to 80°C in a water bath before the carriers and the coating materials were incorporated [Spireas, 1998]. In the present study, the effect was analyzed and as depicted in the Fig. 4.9 the difference in the release profile of liquisolid compact having PG as a solvent was not significant but a relatively significant difference was observed in case of PEG 400 which could be due to the lower solubility of the drug in the solvent ($P < 0.05$). Similar results were reported by Nokhodchi *et al*. (2005).

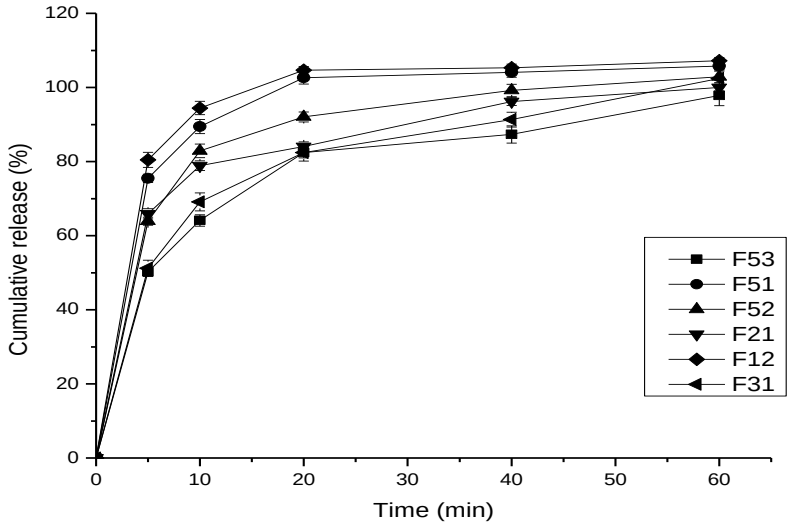

Figure 4.9*: In vitro* diclofenac sodium release profile from Formulation 5 showing the effect of heating (F51, F52, F53 were prepared without heating using PG (F51; Avicel® PH101 and F52; Avicel® PH200) PEG 400 (F53; Avicel® PH101). F12, F21, F31 were prepared by heating the solution using PG (F12; Avicel® PH101 and F21; Avicel® PH200) PEG 400 (F31, Avicel® PH101)

4.4 Sustained release liquisolid compact of diclofenac sodium

4.4.1 Powder and tablet properties of sustained release liquisolid compacts

The powder and tablet properties of all the liquisolid compacts were found to be in the acceptable range. The flow parameters associated with Tween 80 had better values than those associated with PG and not statistically significant difference was observed between Eudragit and Avicel® PH101. All the tablets tested took more than 120 min to disintegrate. It was also observed that those liquisolid compact made using Eudragit® RL took more time to disintegrate than those containing Avicel® PH101 as a carrier ($P < 0.05$).

Table 4.8: Powder and tablet properties of sustained release liquisolid compact

Formulation	Hardness (Kg/cm^3)	Friability (%)	Weight variation (mg)	Angle of repose	Disintegration time (min)
FS1	143 ± 1.36	0.53 ± 0.05	486 ± 3.71	29.0 ± 1.01	> 120
FS2	151 ± 4.14	0.51 ± 0.06	372 ± 1.08	28.06 ± 2.3	> 120
FS3	151 ± 0.64	0.50 ± 0.31	411 ± 3.35	28.0 ± 1.3	> 120

N.B. Mean ± SD (n=3)

4.4.2 Drug release profile of sustained release liquisolid compact of diclofenac sodium

The dissolution profiles of the compacts and Voltarene® SR 75 mg were estimated and *in vitro* release profiles of the formulations are shown in Fig. 4.11. It is evident from the figure that the tablets prepared by LS technique showed retardation properties which is comparable with marketed diclofenac sodium. The results showed that the percentage of drug released from liquisolid matrices containing Avicel® PH101 is greater than liquisolid matrices containing the Eudragit® RL. This could be attributed to the difference in water permeability of the polymers.

In preparation of liquisolid tablets, liquid medications containing drug were adsorbed on the surface of carrier materials. Then, when this system is exposed to the dissolution medium, drug located on the surface of tablets dissolves fast and diffuses into dissolution medium. This can be assumed to be the cause of the burst release effect observed within the first hours. The mechanism of release prolongation is likely to be a more efficient encapsulation of drug particles by the hydrophobic polymers. However, a major difference in the liquisolid formulation was due to the presence of Polysorbate 80 (comparing FS1 with FS2 and FS3).

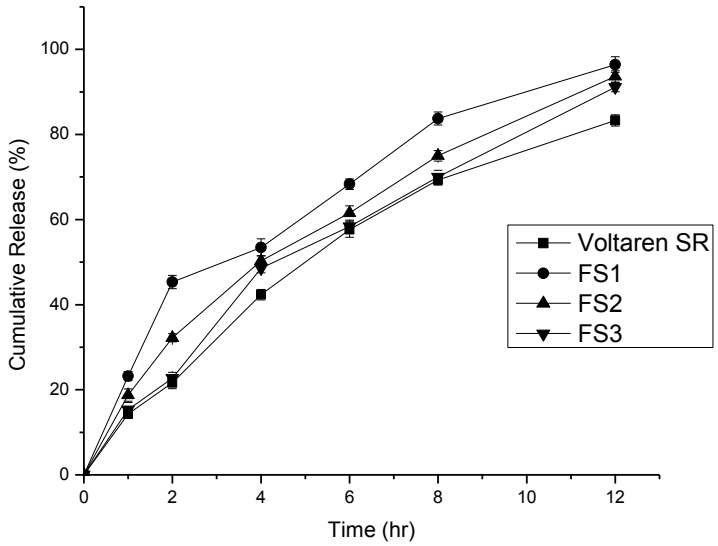

Figure 4.11: *In vitro* diclofenac sodium release profile of sustained release liquisolid compacts (FS1; PG as a solvent and Eudragit RL as a carrier, FS2; Tween 80 as a solvent and Avicel 101 as a carrier, FS3; Tween 80 as a solvent and Eudragit RL as a carrier

An interesting property of Polysorbate 80 is its plasticizer effect by which it can reduce the glass transition temperature (Tg) of polymers and impart flexibility [Javadzadeh *et al*., 2008]. Plasticizers affect the intermolecular bonding between polymer chains, thereby increasing flexibility. Therefore, reduction of Tg of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the Tg, a better coalescence of the polymer particles occurs that forms a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug [Ganesh *et al*., 2011].

A model-independent method such as the similarity factor (f2) provides a simple way to compare dissolution data. Table 4.9 shows f2 values of SRLSC. Although the dissolution profile seems to be equivalent to that of the marketed tablets, differences in f2 values of FS1 might be due to a higher solubility of the drug in the solvent used. Other Formulations had f2 values > 50 indicating a similarity in the dissolution profile.

Table 4.9: Similarity factor (f2) values of liquisolid compacts in comparison to marketed tablets

Comparison	f2	Dissolution Profile
FS1 and Voltarene® SR 75 mg	41.97	Dissimilar
FS2 and Voltarene® SR 75 mg	55.35	Similar
FS3 and Voltarene® SR 75 mg	65.99	Similar

4.4.3 Drug Release kinetics of liquisolid compact of diclofenac sodium

The release mechanisms of the formulations were investigated using various dissolution models; zero-order, first-order, Higuchi, and Hixson Crowell model. The correlation coefficient (R^2) was used to select the best model that best fitted the release data, i.e., the model that gave the highest 'R^2' value (R^2 close to 1) was considered the best fit for the release data [Dash *et al*.,2010]. The 'R^2' values in zero order, first order, Higuchi, and Hixson-Crowell model fittings are given in Table 4.10.

Table 4.10: Correlation coefficients and rate constants of different drug release kinetic models for liquisolid compact

Release model	kinetic parameters	FS1	FS2	FS3	Voltarene SR 75 mg
Zero order	R^2	0.9201	0.9635	0.9549	0.9324
	$K(h^{-1})$	-6.3119	-6.6425	-6.8264	-4.8831
First order	R^2	0.7548	0.8102	0.7600	0.9969
	$K(h^{-1})$	-0.1127	-0.1334	-0.1556	0.1497
Higuchi	R^2	0.9718	0.9987	0.9958	0.9902
	$K(h^{-1/2})$	28.929	30.222	31.132	22.4309
Hixson-Crowell	R^2	0.9823	0.9891	0.9864	0.9875
	$K(h^{-1/3})$	-0.2394	-0.2188	-0.2052	-0.1563

The liquisolid formulations exhibited best fit for Higuchi equation with R^2 value greater than 0.99 except FS1, the latter formulation showed best fit for Hixson-Crowell model which is due to a relatively high drug release rate at initial phase followed by a phase in which the decrease of the release rate is more pronounced.

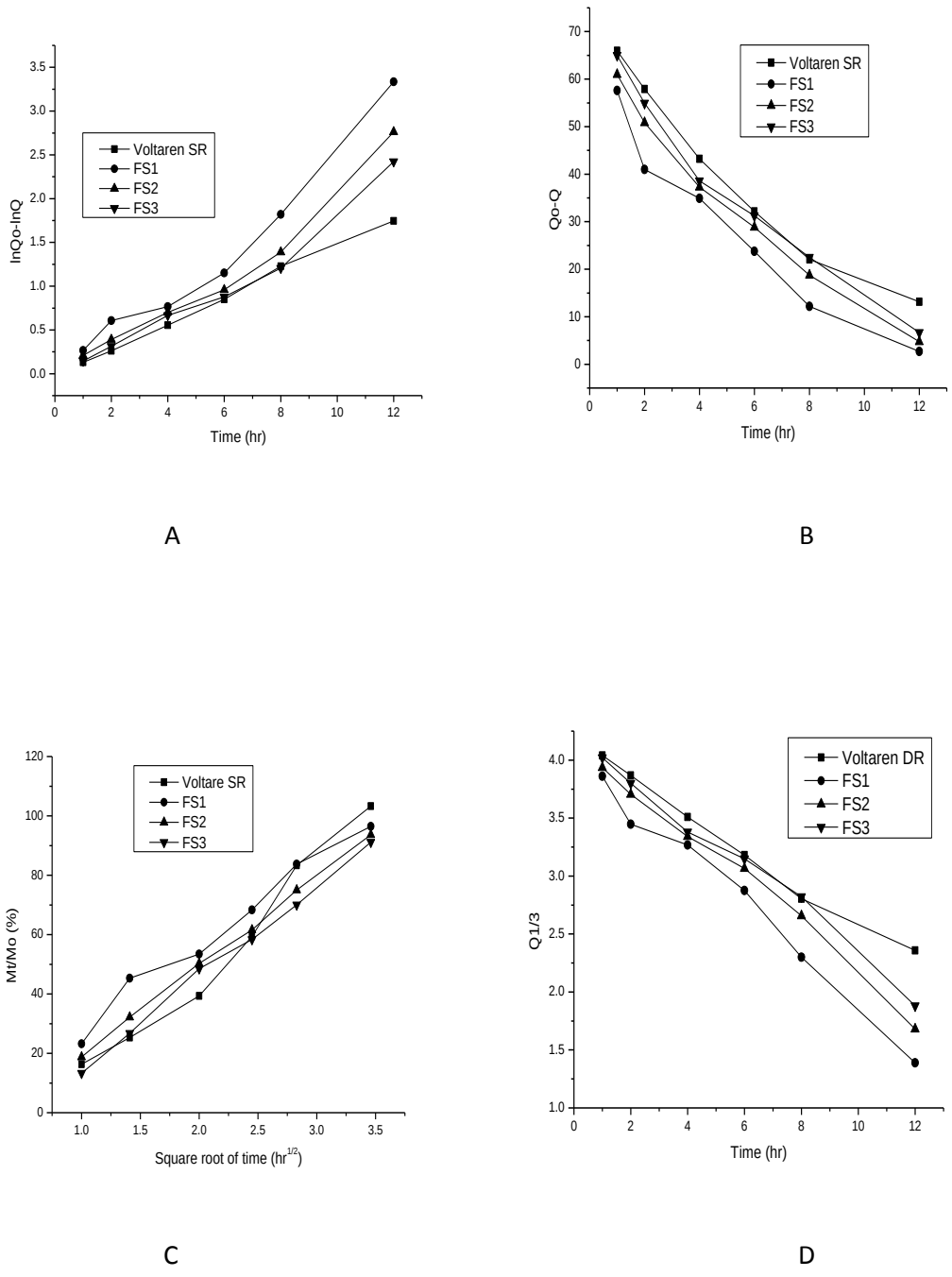

Figure 4.11: Kinetic model of liquisolid compact (First order release model (A), zero order release model (B), Higuchi release model (C) and Hixson-Crowell release model (D))

To find out the mechanism of drug release, the first 60% drug release data were fitted in to Korsmeyer Peppas model in which the value of *n* characterizes the release mechanism of the

drug. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

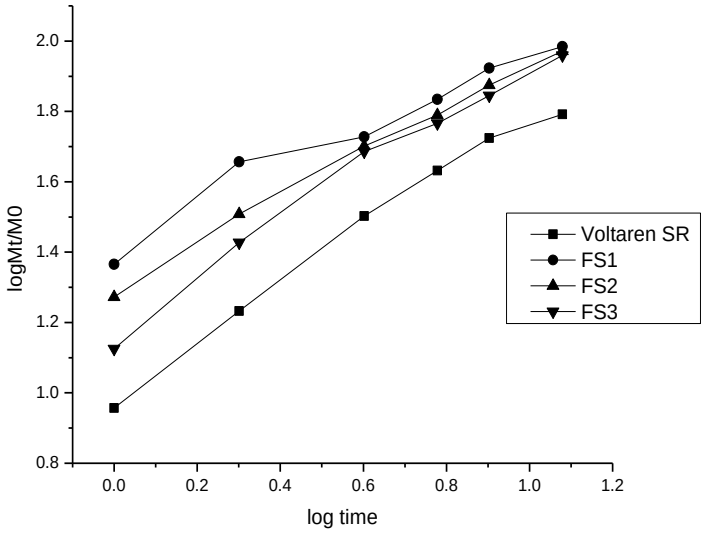

Figure 4.13: Korsmeyer-Peppas release model fitting of drug release SRLSC

Based on the results of this study the mechanism of drug release from liquisolid compact is non Fickian diffusion. All formulations containing polysorbate 80 showed higher n ($P < 0.05$) values than those with PG (0.58). This indicates that the contribution of erosion in liquisolid compact is more than the contribution of diffusion. It was also observed that the value of n for FS2 is higher than that of FS3 ($P < 0.05$) implying erosion as a mechanism of release in case of hydrophilic polymer.

5. CONCLUSION

The foregoing results demonstrate the liquisolid technology could be used as a tool to enhance as well as sustain the release of diclofenac sodium. It was also observed that modifying the variables in the formulation gave the desired release profile. Higher dissolution rate liquisolid diclofenac sodium compacts displayed acceptable powder and tablet property throughout the study. Parameters such as the type of solvent and the carrier; the ratio of the carrier to coating material; the concentration of the liquid medication; the type of disintegrant and the effect of heat treatment were evaluated and all were found to influence the *in vitro* drug release of DS. The liquisolid compact of DS made in PG showed better dissolution rate than DS with PEG 400 based upon solubility and molecular fraction (FM) of the drug in their liquid medication. Drug release of liquisolid compact prepared with Avicel® PH101 was found to be higher than those of Avicel® PH200. As R-value increased the dissolution rate was found to be enhanced. It was also observed that heat treatment had no major effect on release profile of drug from liquisolid tablets. The present work showed that liquisolid technique can be optimized for the production of sustained release matrices. Furthermore, this study has shown that Tween 80 has important role in sustaining the release of drug from liquisolid matrices. In summary, the technique can be used in the preparation of enhanced and sustained release formulations of drugs such as diclofenac sodium.

6 SUGGESTION FOR FURTHER WORK

Based on the results of this study, further investigation in the following directions is suggested:

- Evaluating the effect of coating material
- Studying the effect of highly effective tableting excipients for liquid adsorption on the liquisolid compact
- Comparing liquisolid technology with other established dissolution enhancing methods
- Evaluating the effect of formulation material on the *in vitro* release of drug from the sustained release liquisolid compact
- *In vivo* evaluation of the formulations

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