A review on

“Development of dissolution medium of poorly soluble drug by using surfactants”

A project

Submitted by:

ID: 11146001

Session: Spring 2011

Submitted to:

The Department of Pharmacy

In partial fulfillment of the requirements for the degree of bachelor of Pharmacy

BRAC University

Dhaka, Bangladesh

August 2015

Certification Statement

This is to certify that this project titled 'Development of dissolution medium of poorly soluble drug by using surfactants' submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Shahana Sharmin, Senior lecturer, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed

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Countersigned by the supervisor

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Dedicated to my parents, who sacrificed their every desire since my birth and inspire me in every steps of my life.

Acknowledgment

I would like to express my thanks and gratitude to the Department of pharmacy, BRAC University for the completion of the project. I am also thankful to my supervisor, for her supervision and obliged to all those who have given me their valuable time and energy from their hectic work schedule to express their full experience about the working procedures.

I specially acknowledge her for her support and help throughout my project paper.

- **Ms. Shahana Sharmin**, Senior Lecturer, Department of Pharmacy, BRAC University.

Abstract

The drug dissolution from its dosage form is considered as an important parameter in the absorption. Drugs which are fairly soluble in gastrointestinal (GI) media exhibit complete oral absorption leading to better bioavailability. For BCS class II drug, solubility is a crucial rate limiting factor to achieve its desired level in systemic circulation for pharmacological response. In this review article, study shown to improve the drug solubility by adding surfactant into the dissolution media. Especially we have found the solubility data on the drugs having low solubility like Glipizide, Carvedilol, Carbamazepine, Mefenamic acid, Simvaststin, Candesartan Cilexetil and Ibuprofen. For the improvement of their dissolution medium surfactants like SLS, Tween 80, SDS are being used. For Glipizide, Carvedilol, pure Carbamazepine, CBZ–NIC co crystal and the physical mixtures of CBZ III and NIC, Simvastatin, Mefenamic acid, Ibuprofen and Candesartan Cilexetil the highest solubility was found in the medium containing 0.75% SLS in phosphate buffer pH 6.8, 3% SLS in water and 3% SLS in 0.1 N HCL, 10.4 mM SLS in water, 0.1% SLS in water, 2% w/v of SLS, 0.1% SDS in phosphate buffer pH 7.2 and 0.35% w/v Tween 20 in phosphate buffer pH 6.5 respectively.

List of Abbreviation

BCS- Biopharmaceutical Classification System

USP- United States of pharmacopoeia

BP- British pharmacopeia

FDA- Food and drug administration

IR- Immediate release

SLS- Sodium lauryl sulfate

CBZ- Carbamazepine

CBZ–NIC- Carbamazepine–nicotinamide

CBZ DH- Carbamazepine dihydrate

CMC- Critical micelle concentration

NIC- Nicotinamide

HPLC- High-performance liquid chromatography

HPMC- Hydroxy propyl methyl cellulose

DSC- Differential scanning calorimetry

TGA- Thermogravimetric analysis

RPM- Rotation per minute

CTAB- Cetyltrimethyl ammonium bromide

CT- Carvedilol tablet

DM- Dissolution medium

DR- Drug release

IDR- Intrinsic dissolution rate

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Chapter 1:

1.1 Introduction

Dissolution study is one of the most essential tests as it determines quality of product and behavior of drug release (Shah *et al*., 1989; Dressman *et al*., 1998; Pillay & Fassihi, 1998). The purpose for this test is that in order to be absorbed the drug it should be properly dissolved within the gastrointestinal tract.

Drug dissolution involves two important points, transport of drug within the dissolution medium and release of drug from the dosage form. A number of factors influence drug dissolution including:

- Physic-chemical properties of drug(e.g. Solubility of drugs, particle size of the drugs, molecular structure of the drugs, crystalline forms in the dissolution medium),
- Formulation characteristics (e.g. additives, coating materials, manufacturing parameters),
- Dissolution techniques (e.g., apparatus type, surface tension, ionic strength, volume, viscosity and pH of the medium and hydrodynamic environment), (Abdou, 1989).

For low soluble drugs, dissolution study is particularly important especially for class II drugs according to Biopharmaceutical Classification System. The development of a dissolution technique for this group of drug is quite challenging. Dissolution medium must give sink conditions; also the drug concentration in the dissolution medium should not exceed 15 to 20 % of saturation solubility of the drug in order to give sink conditions (Carstensen, 1977; Amidon *et al.*, 1995). Absence of sink conditions may result in uncertain release kinetics and suppression of release profiles. Different approaches have been recommended for designing dissolution tests for poorly water soluble drugs. The approaches are (Banakar, 1992; Jinno *et al.*, 2000; Tang *et a.*, 2001; Noory *et al.*, 2002):

- Use of large volume of dissolution medium,
- By removing of dissolved drug,
- Mixing organic aqueous solvents,
- Two phase dissolution media with an upper organic layer,
- The addition of surfactants,
- PH changes.

Moreover, the GI environment must be simulated in a well designed dissolution testing and any modification is applicable towards real GI conditions. Among the mentioned conditions, adjustment of pH and addition of surfactant appear to be the simplest and can be modified to resemble GI fluid environment.

1.2 Drug Solubility

Solubility is the property of a liquid, solid or vaporous substance material called solute to dissolve in a liquid, solid or vaporous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally relies on upon the solvent utilized also depends on temperature and pressure. The level of solubility of a substance in a specific solvent is measured as the saturation concentration where addition of more solute does not improve its concentration in the solution. (Lachman *et al.*, 1986)

The solvent is unadulterated generally a liquid or a mixture of two liquids. Solvent may be solid solution, however once in a while of solution in a gas. The measure of solubility ranges widely, from infinitely soluble (completely miscible) like ethanol in water and poorly soluble like silver chloride in water. The term insoluble is regularly connected for poorly or very poorly soluble compounds. (Clugston & Fleming, 2000)

Under dynamic equilibrium solubility may happens, which implies that solubility results from the concurrent and restricting procedures of dissolution and phase joining (e.g., precipitation of solids). At the point when the two procedures continue at a steady rate, solubility equilibrium occurs. Under specific conditions equilibrium solubility may be surpassed to give so called supersaturated solution, which is Meta stable. (Myrdal & Yalkowsky, 2007)

Solubility is not to be mistaken for the capacity to melt or dissolve a substance due to dissolution as well as chemical reaction all of these procedures may happen. Case in point, zinc is insoluble in hydrochloric acid, yet by chemically reacting into zinc chloride and hydrogen it does dissolve in it, where zinc chloride is soluble in Hydrochloric acid. Solubility does not rely on upon molecule size or other active components. By giving adequate time, even expansive particles will in the long run dissolve. (Martin, 2011)

Broad utilization of solubility from alternate point of view has prompted solubility being expressed in different ways. It is generally expressed as a concentration, either by mass, morality, molarity, mole fraction or other other identical descriptions of concentration. The maximal equilibrium amount of solute to dissolve per measure of solvent is the solubility of that solute in that solvent under the specific conditions. (Aulton, 2002).The point of interest of expressing solubility in this way is its straightforwardness and the disadvantage is that it can firmly rely on upon the presence of different species in the solvent.

Saturated solutions of ionic compounds of low soluble drugs are in some cases portrayed by solubility constants which are known as the equilibrium process. It depicts the balance between undisclosed salt and a dissolved ion from the salt. The scientific estimation of solubility consistent is affected by temperature and other equilibrium constants. From different species in the solvent, the estimation of this constant is generally independent. The Flory-Huggins arrangement hypothesis is a hypothetical model describing the solubility of polymers. The Hildebrand solvency parameters and the Hansen Solubility Parameters are exact systems for the estimation of solubility. It is additionally conceivable to quantify the solubility from other physical constants, for example, the enthalpy of fusion. The partition coefficient (Log P) is a measure of differential solubility of a compound in a hydrophobic solvent (octanol) and a hydrophilic solvent (water). The logarithm of these two qualities facilitates compounds to be positioned as far as hydrophobicity or hydrophilicity (The United States Pharmacopeia, 2007; British Pharmacopeia, 2009).

1.3 Dissolution Apparatus

The dissolution testing which is directed in dissolution apparatus must have the capacity to give precise and reproducible results. A few dissolution apparatuses exist. As indicated by United States Pharmacopeia (USP) there are four apparatuses standardized and specified (United States Pharmacopeia, 2011).

They are:

- USP Dissolution Apparatus 1 - Basket (37°C)
- USP Dissolution Apparatus 2 - Paddle (37°C)
- USP Dissolution Apparatus 3 - Reciprocating Cylinder (37°C)
- USP Dissolution Apparatus 4 – Flow through Cell (37°C)

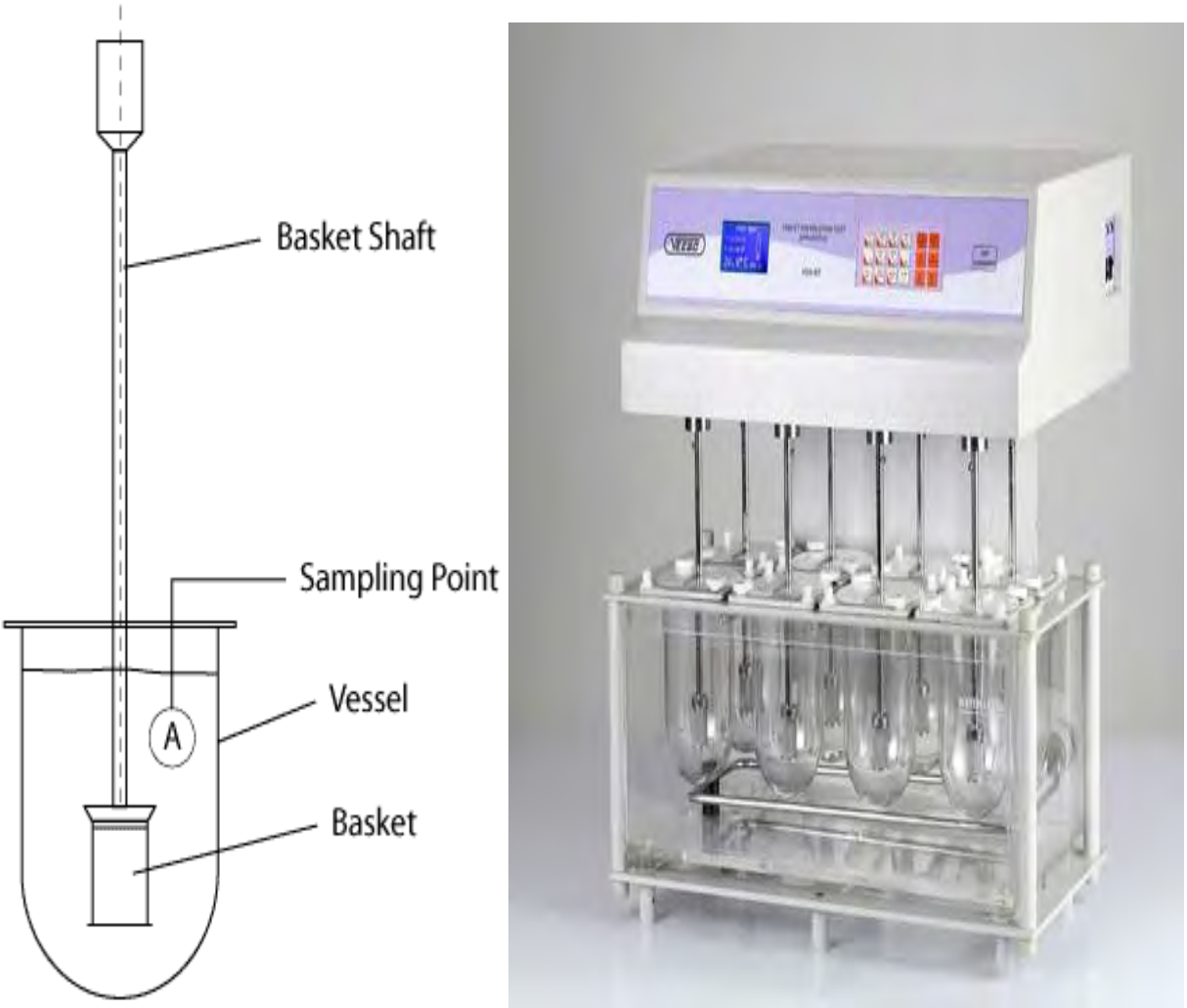


Figure 1.1: USP Dissolution Apparatus 1-Basket method (http://goo.gl/wNz0z1 & http://goo.gl/HY4Yda).

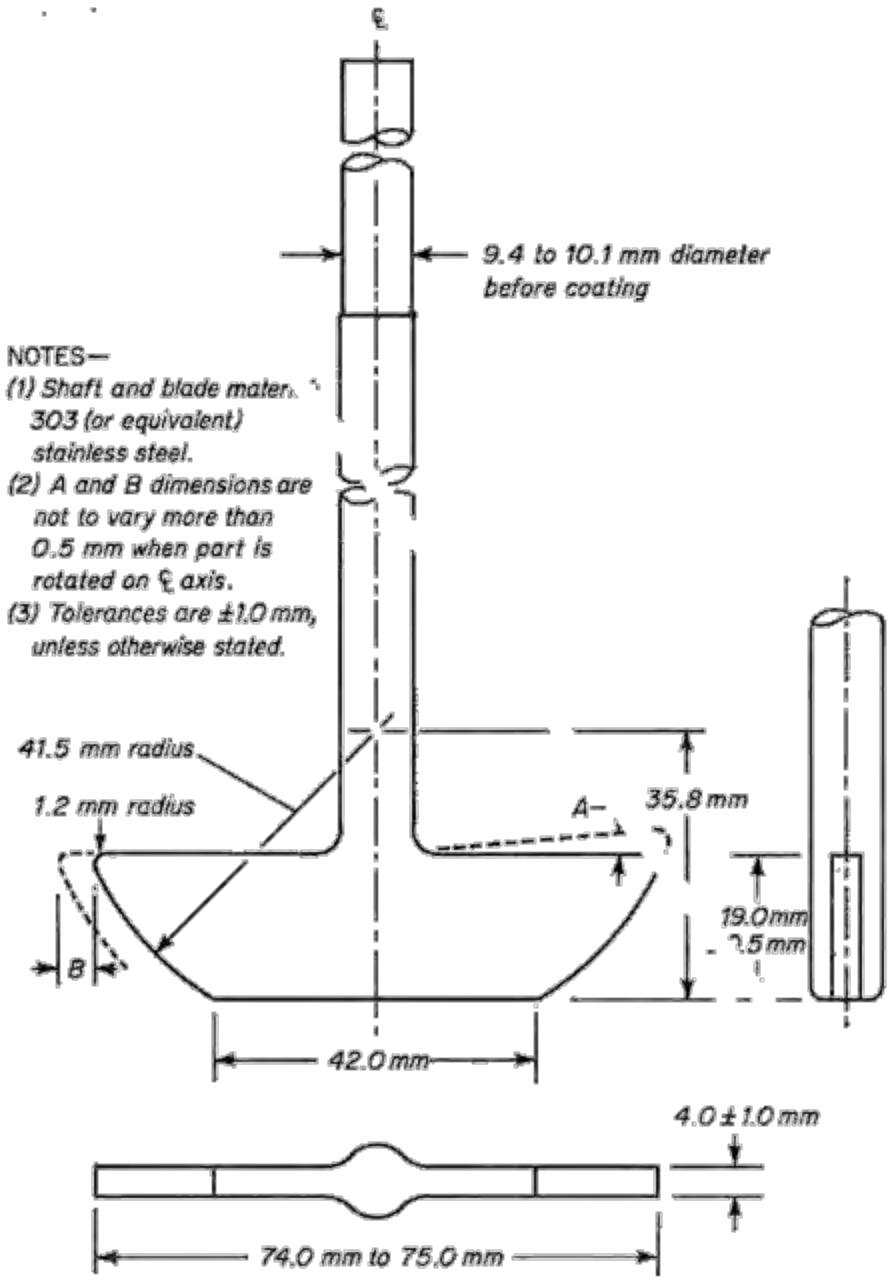


Figure 1.2: USP Dissolution Apparatus 2 -Paddle method (http://goo.gl/qnfHZN).

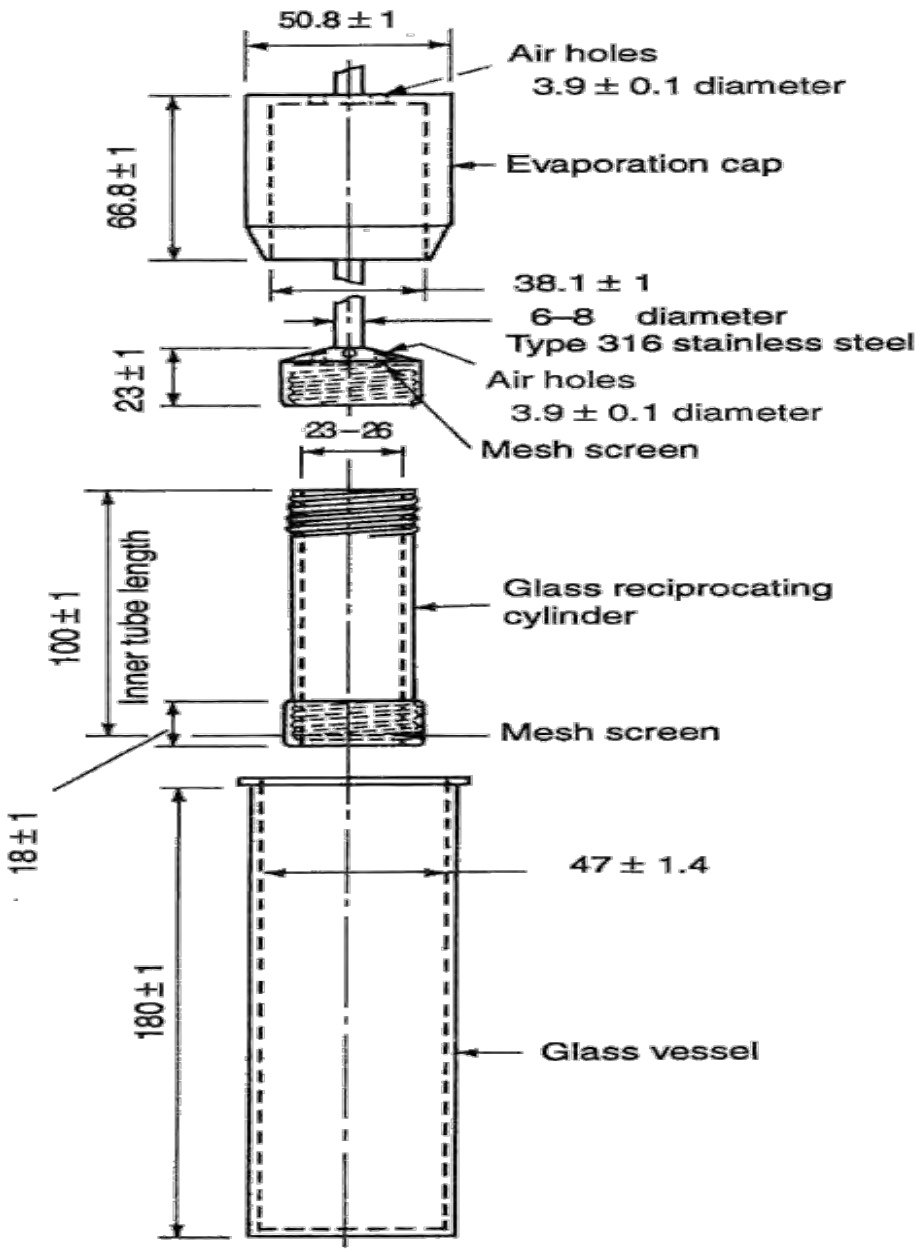


Figure 1.3: USP Dissolution Apparatus 3-Reciprocating Cylinder (http://goo.gl/693nUG).

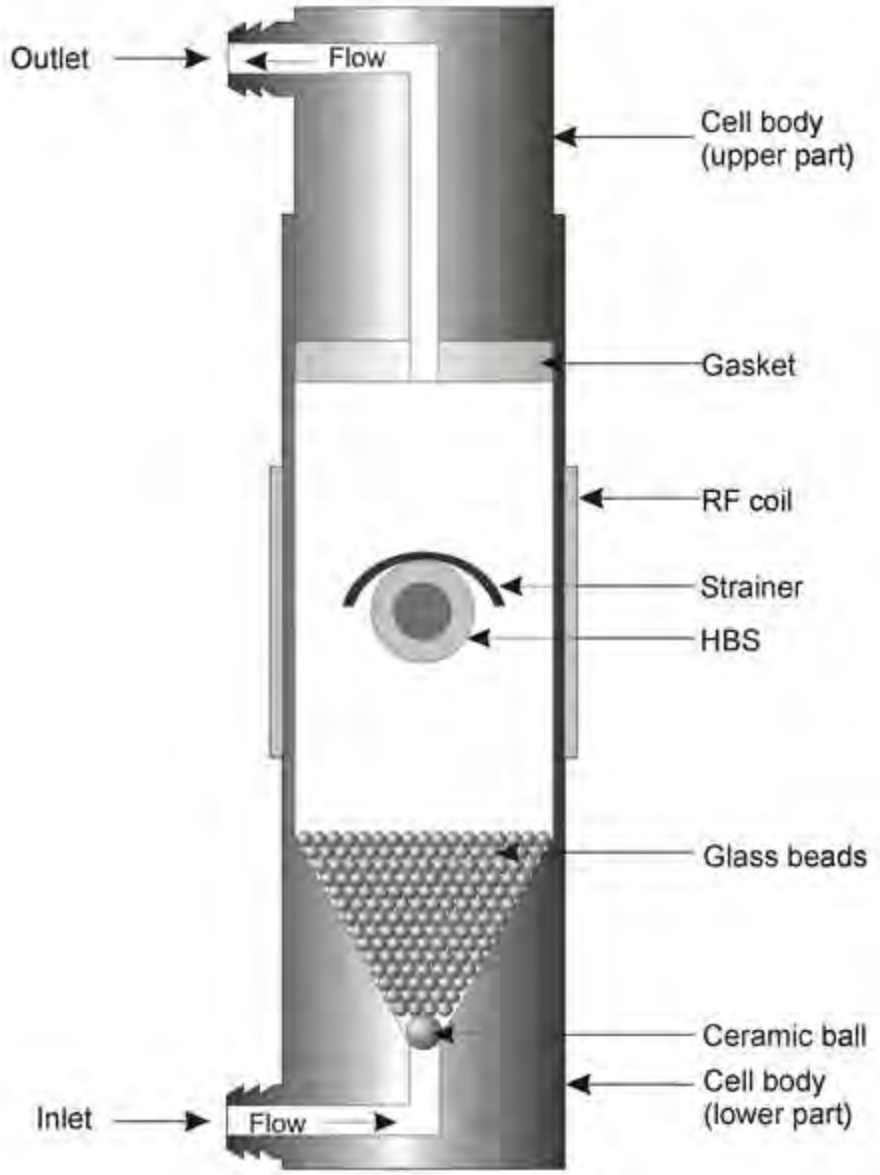


Figure 1.4: USP Dissolution Apparatus 4-Flow through Cell (http://goo.gl/aS7ups).

1.4 Biopharmaceutics classification system

Biopharmaceutics classification system (BCS) is a logical classification of a drug substance taking into accounts its aqueous solubility and intestinal penetrability that connects in vitro disintegration and in vivo bioavailability of drug products. (Amidon, 1995; Wagh & Patel, 2010).When consolidated with in vitro dissolution qualities of the drug product, BCS consider two central point: solubility and intestinal permeability, which control the rate and degree of oral drug absorption from solid dosage forms and eventually its bioavailability (British Pharmacopeia, 2009). Because of this reason, BCS is the crucial tool in the drug development particularly in the development of oral drug products.

The food and drug administration (FDA) foundation for solubility characterization of a drug in BCS is in view of the highest dose strength in an immediate release (IR) oral product (Yu et al., 2002). A drug is considered exceedingly soluble when the highest strength is soluble in 250 ml or less of watery media over the pH 1.0 to 7.5; generally the drug substance is viewed as poorly soluble drug. In addition the permeability classification is construct specifically with respect to the degree of intestinal absorption of a drug substance in people or in a indirectly on the estimations of the rate of the mass exchange over the human intestinal layer or in creatures or in vivo models (Wagh & Patel, 2010; Yu et al., 2002). A drug substance is considered highly permeable when the degree of intestinal absorption is absorption to be 90% or higher taking into account mass-equalization or in correlation to an intravenous reference dose.

The bioavailability of BCS class II drugs dissolution rate are lower. But due to high permeability, the BCS class II drugs have been used for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed (Kumar *et al.*, 2013; Onoue *et al.*, 2012; Urbanetz, 2006; Fahr & Liu, 2007). In case of class III drugs, the bioavailability of drugs are rate limited, but dissolution is likely to occur promptly. Thus for class III drugs, formulating IR solid dosage forms with absorption enhancers can be a viable formulation option to improve their permeability (Pouton, 2006).

But in case of BCS class IV compounds, both dissolution and permeability are limited. Because of the low membrane permeability, BCS class IV drugs are often poor competitor for drug development since solubility and dissolution enhancement alone might not help improve their bioavailability.

However, these classes of compounds cannot be ignored just because of their permeability matter. Therefore the current approaches being used for BCS class II drugs, with absorption enhancers, can be applied to formulate class IV compounds. (Martin, 2011). Another formulation development approach for class IV compounds is the selection of a better drug candidate with more appropriate physiochemical properties during the lead optimization phase (Urbanetz, 2006; Fahr & Liu, 2007).

Table 1: Bio pharmaceutics classification system (BCS) with characteristics of drugs.

BCS class	Solubility	Permeability	Absorption pattern	Examples
1	High	High	Well absorbed	Metoprolol,diltiazem,propranolol
2	Low	High	Well absorbed	Phenytoin ,nifedipine, danazol
3	High	Low	Variable	Cimetidine, captopril
4	Low	Low	Poorly absorbed	Taxol,furosemide

1.5 BCS class 2 drug lists ("PharmPK Discussion List", 2009)

Amiodarone	Cyclosporine	Indomethacin	Itraconazole
Atorvastatin	Danazol	Phenazopyridine	Ketoconazole
Azithromycin	Dapsone	Phenytoin	LansoprazoleI
Carbamazepine	Diclofenac	Indinavir	Lovastatin
Carvedilol	Diflunisal	Spironolactone	Mebendazole
Chlorpromazine	Erythromycin	Raloxifene	Naproxen
Cisapride	Flurbiprofen	Saquinavir	Nelfinavir
Ciprofloxacin	Glipizide	Sirolimus	Ofloxacin
Griseofulvin	Glyburide	Tacrolimus	Oxaprozin
Ibuprofen	Terfenadine	Tamoxifen	Talinolol
Piroxicam	Ritonavir	Isoniazid	Mefenamic acid
Simvastatin	Candesartan Cilexetil		

Chapter 2: Research Methodology

The review article is focused on the current status of drug release of poorly water soluble drug in an improved dissolution media by the addition of surfactant is summarized. The literature search was performed using the "Web of Science" (ISI). The keywords "Surfactant" and "dissolution media" and "poorly water soluble drug" gave 1517 hits for the period from 1990 to 2015. The results were further cross checked by searching through Elsevier's "Science Direct", PubMed, SpringerLink, and Informa world. Other references and conference proceedings have also been included.

Presently there is a great interest in developing dissolution medium for insoluble drug by using surfactant especially for BCS class-II type of drugs. Biopharmaceutics classification system (BCS) has been evaluated as it is a scientific classification of a drug substance based on its aqueous solubility and intestinal permeability that correlates in vitro dissolution and in vivo bioavailability of drug products. The bioavailability of BCS class II drugs is likely to be dissolution rate limited but due to their high permeability, the BCS class II drugs have been on focus for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed. Therefore, the knowledge of dissolution behavior and the factors affecting such performance are of paramount importance in design, evaluation, control and therapeutic efficacy of solid dosage forms. The bioavailability of the orally administered drugs that are practically insoluble is usually less. Since the limiting step in vivo absorption process of such drugs is their dissolution rate, there is a definite need for the development of an appropriate dissolution test. However there is no specific surfactant to be used. Surfactants that are Sodium Lauryl Sulfate, Tween 80, Tween 60 and so on. Moreover, the development of dissolution media whether for better drug release of BCS class-II drugs requires efficient surfactant in sufficient percentage. The water solubility of a drug is a fundamental property that plays an important role in the absorption of the drug after oral administration. As such surfactant can solubilize and improve the release rate which is often associated with the effect of increasing the hydrophilicity thereby promoting drug dissolution. The presence of surfactant influenced the tablet disintegration rate, producing a finer dispersion of disintegrated particles.

The purpose of this review is to discuss about the improvement of dissolution by adding different surfactants in different concentration in the dissolution media for different types of poorly soluble drugs.

Chapter 3: Result and discussion

3.1 Glipizide

After reviewing the literatures worked on Glipizide we found that

3.1.1 For Glipizide: Article 1 (Jamzad& Fassihi, 2006)

Material	Method
• Glipizide • Hydroxypropylmethyl cellulose(HPMC) • Tween 80 • Sodium lauryl sulfate (SLS) • Buffer ingredients • Deionized water • Glipizide controlled-release matrix tablet	**Saturation Solubility Studies:** • **Medium:** 100 ml volumetric flask • **Temperature:** 25^0C • **P^H of medium:** ➢ HCl/KCl buffer pH: 2 ➢ Acetate buffer pH: 4.4 ➢ Demonized water pH: 5.2 ➢ Phosphate buffers pH: 5.8, 6.8, 8 and 10 **Dissolution Studies:** • **Dissolution medium**: 900 ml • **Temperature**: 37ºC • **Dissolution medium**: 900 ml • **Apparatus**: USP apparatus 2 (paddle) • **Rotational spread**: 75 rpm • **Filter**: 35-µm filters • **Absorbance measured by**: Cary-50 UV-vis spectrophotometer at 276 nm.

3.1.2 For Glipizide: Article 2 (Mandal et al., 2008)

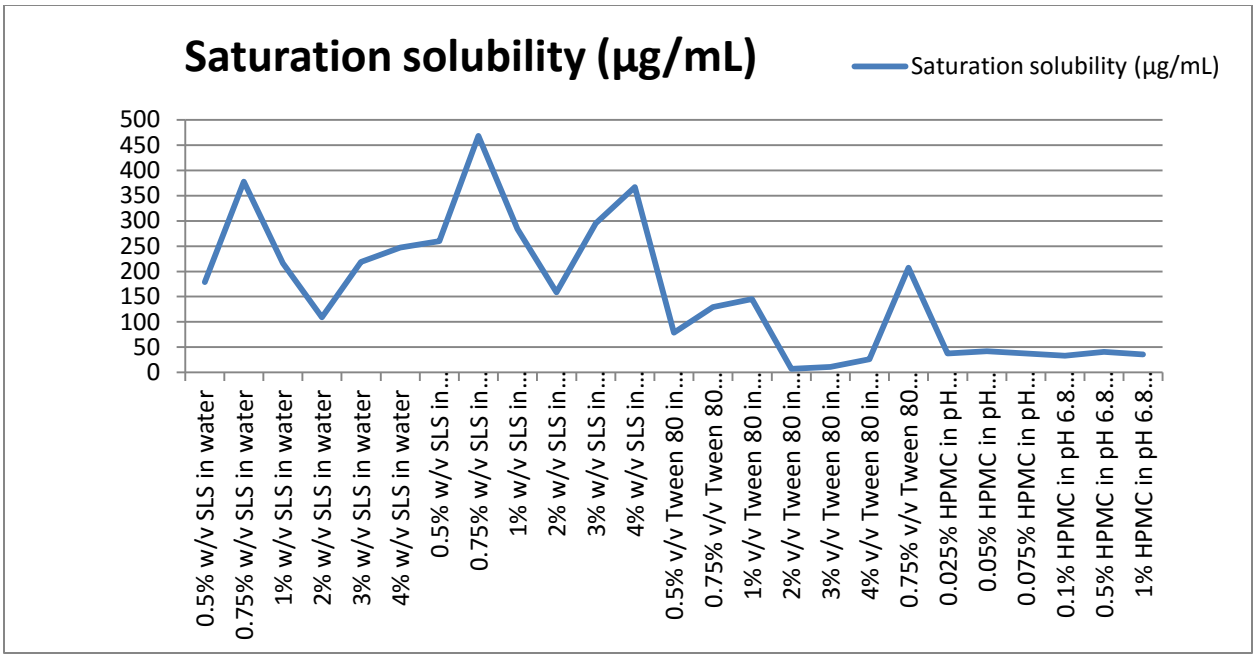
Material	Method
• Glipizide • Three marketed brands of glipizide tablets • Sodium lauryl sulphate (SLS) • Tween 80 • Methanol • Deionized water • 10 mg immediate release tablets of glipizide (Glipicontin).	**Saturation solubility study:** • **Temperature**: 37 ± 0.5 ºC. • **Filter**: 45 µm mille pore. • **Analyzed by**: UV-Vis spectrophoto-meter at 276 nm. **Dissolution study:** • **Dissolution Apparatus**: USP Dissolution Apparatus II • **Temperature**:37± 0.5 ºC • **Rotational speed**: 45 rpm. • **Filter**: 0.22 µm Milipore. • **Method**: UV method.

Table 3.1: In different dissolution medium Saturation Solubility & Relative Sink Condition (Cs/Cd) of Glipizide.

Dissolution media	Saturation Solubility (µg/mL)	Relative Sink Condition, CS/CD (10 mg tablet)
0.5% w/v SLS in H_2O	179.06	1.31
0.75% w/v SLS in H_2O	378.02	2.86
1% w/v SLS in H_2O	216.25	1.43
2% w/v SLS in H_2O	108.99	0.95
3% w/v SLS in H_2O	218.67	1.73
4% w/v SLS in H_2O	247.40	2.25
0.5% w/v SLS in phosphate buffer (pH 6.8)	260.12	2.32
0.75% w/v SLS in phosphate buffer (pH 6.8)	468.27	4.89
1% w/v SLS in phosphate buffer (pH 6.8)	283.71	2.41
2% w/v SLS in phosphate buffer (pH 6.8)	158.32	1.23
3% w/v SLS in phosphate buffer (pH 6.8)	295.43	2.47
4% w/v SLS in phosphate buffer (pH 6.8)	367.20	2.63
0.5% v/v Tween 80 in H_2O	78.74	0.87
0.75% v/v Tween 80 in H_2O	129.35	1.13
1% v/v Tween 80 in H_2O	145.24	1.19
2% v/v Tween 80 in H_2O	7.35	0.04
3% v/v Tween 80 in H_2O	11.04	0.09
4% v/v Tween 80 in H_2O	26.01	0.19

Table 3.1 (continued) :

Dissolution media	Saturation Solubility (µg/mL)	Relative Sink Condition, CS/CD (10 mg tablet)
0.75% v/v polysorbate 80 (Tween 80) in phosphate buffer (pH 6.8)	207.00	1.39
0.025% HPMC in pH 6.8 Buffer	37.30	3.36
0.05% HPMC in pH 6.8 Buffer	42.02	3.78
0.075% HPMC in pH 6.8 Buffer	37.80	3.40
0.1% HPMC in pH 6.8 Buffer	32.90	2.96
0.5% HPMC in pH 6.8 Buffer	40.50	3.65
1% HPMC in pH 6.8 Buffer	35.40	3.19



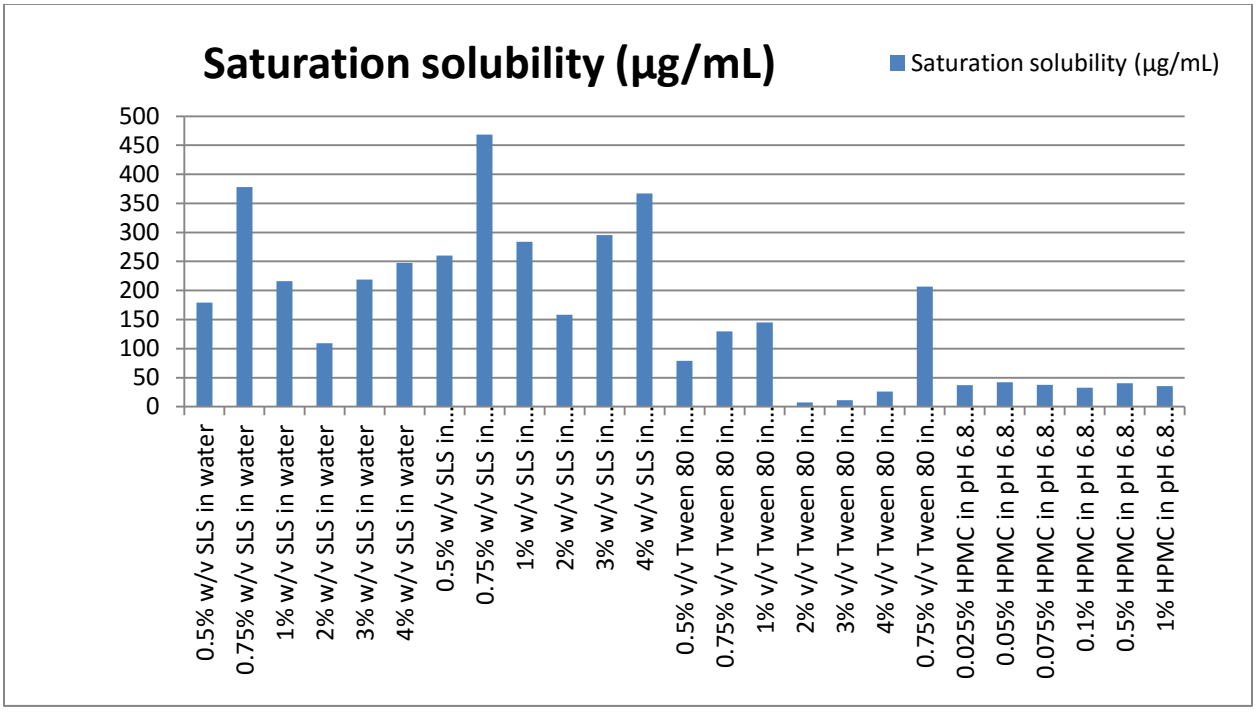
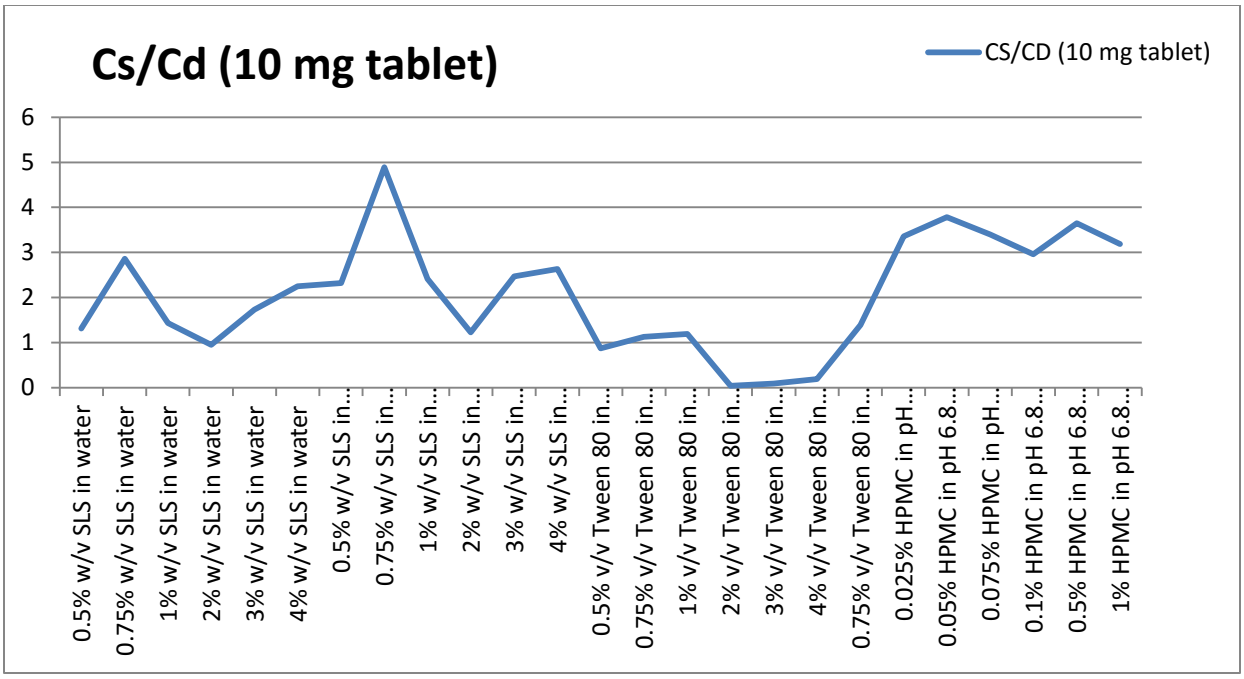


Figure 3.1.1: Saturation solubility of Glipizide



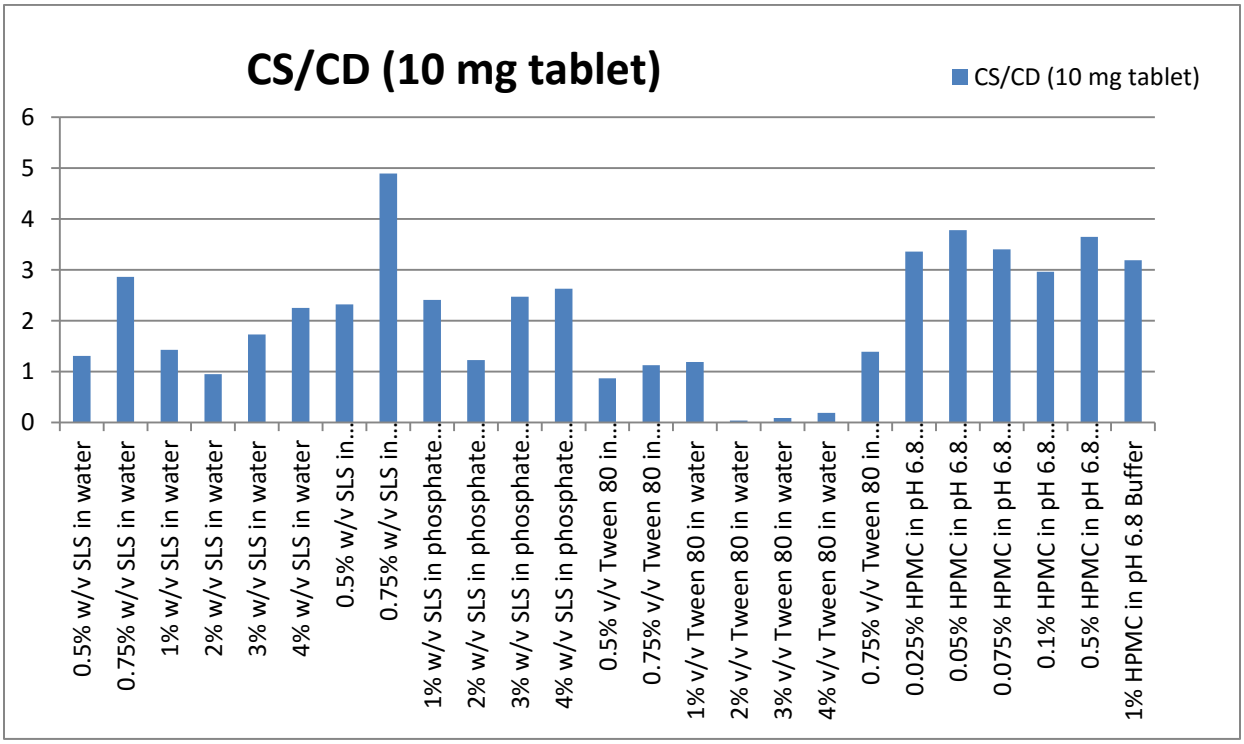


Figure 3.1.2: Relative Sink Condition (CS/CD) over drug concentration

Glipizide is a weak acid and its pKa is 5.9. The solubility is required to increase with the increaseincreaseof pH; however at higher pH it may not be bio-significant. In Table-3.1 the saturation solubility (Cs) of glipizide at diverse dissolution media alongside comparing Relative Sink Condition (Cs/Cd) values where Cd refers to concentration of glipizide after complete dissolution of tablet in 900 mL dissolution medium.

Saturation Solubility and Relative Sink Condition (Cs/Cd) of Glipizide from different articles, for SLS in water has shown (108.99-378.02) µg/mL and (0.95-2.86); for SLS in phosphate buffer has shown (158.32-468.27) µg/mL & (1.23-4.89) ; for Tween 80 in water has shown (7.35-145.24) µg/mL and (0.04-1.19); for hydroxypropyl methyl cellulose (HPMC) has shown (32.90-42.02)) µg/mL and (2.96-3.78) and In 0.75% v/v Tween 80 in phosphate buffer (pH 6.8) has shown 207.00 µg/mL and 1.39 respectively.

The solubility data shown in Table 3.1 that the solubility of drug was found to be highest in the medium containing 0.75 % SLS in phosphate buffer having pH 6.8 (468.27 µg/mL). This data also indicated that the solubility of glipizide in 900 mL of 0.75 % SLS in phosphate buffer having pH 6.8 has shown 4.89 times the solubility of the original dose of glipizide (10 mg).

As 900 mL of 0.75 % SLS in phosphate buffer of pH 6.8 which are thought to be a suitable dissolution medium in light of the fact that it fulfilled the sink condition. The outcomes showed that the dissolution rate of glipizide increase with increase in SLS content in phosphate buffer of pH 6.8 up to 0.75 % (w/v). Addition of surfactant to the dissolution medium enhances the dissolution of pure drug by encouraging the drug release process at the solid/liquid interface and micelle solubilization in the mass.

In Table 3.1, solubility of glipizide at diverse concentrations of HPMC was likewise examined. A critical increment in solubility shown in the concentrated range studied. This can be credited to the surface movement of the polymer. ("Dow Chemical Company", 2002)

This diminishment in surface pressure can build the wetting of the drug particles and solubility increments. The adjustment in the solubility at levels over 0.05 mg/mL HPMC may be characterized to the adjustment in the consistency of the medium.

It is usually documented that in vitro dissolution tests ought to have the capacity to anticipate in vivo drug release. For a low solubility drug, increment in solubility by addition of surfactants to meet sink conditions (taking into account mass drug solubility information) may not generally deliver bio-relevant results (Tang et al., 2001).

3.2 Carvedilol

After reviewing the literatures worked on Carvedilol we found that

3.2.1 For Carvedilol: Article 1 (Babu and Raju, 2009)

Material	Method
• Carvedilol • Sodium Laural Sulphate (SLS) • Tween 80 • Two available brands of Carvedilol tablets used: ➢ Brand A: Cardace 12.5 mg tablet and ➢ Brand B: Cardivas 12.5mg tablet	**Solubility determination:** • **Temperature**: (28 ± 1^0 C) room temperature • **Flask**: Rotary flask • **Filter**: 0.45 µm millipore membrane filter • **Absorbance measured :** at 240 nm **Dissolution rate study:** • **Temperature**: 37ºC • **Dissolution medium**: **DM1:** 0.1 N hydrochloride acid containing 1.0% SLS **DM2:** Distilled water containing 1.0% SLS • **Dissolution apparatus:** USP dissolution apparatus II • **Observed time (min):** 5,10,15,30,45 & 60 • **Rotational speed**: 50 rpm. • **Filter**: 0.45µm millipore filter • **Measuring absorbance**: UV method at 240 nm.

3.2.2 For Carvedilol: Article 2 (Shah et al., 2011)

Material	Method
Chemicals: • Carvedilol BP • Hydroxy propyl methyl cellulose • Polyox WSR 205 • Microcrystalline cellulose • Magnesium stearate • Talc • Sodium starch glycollate • Starch • Disodium hydrogen orthophosphate • Citric acid • Hydrochloric acid • Sodium lauryl sulfate (SLS) **Equipment and instruments:** • Electronic balance • Hardness tester • Tablet compression machine • Roche friabilator • UV Spectrophotometer • Dissolution test apparatus TDT-06T and • laboratory stirrer	**Solubility test:** • In distilled water • **Hydrochloric acid solution pH**: 1.2 • **Citric-Phosphate buffer pH:**4.5, 6.8, 7.4 • **SLS concentration**: 0.1%, 0.5%, and 1.0%. • **Filter**: Whatman 0.45 micron • **Analyzed by:** UV spectrophotometer at 286 nm. **Dissolution test parameter :** • **Dissolution apparatus**: TDT-06T dissolution apparatus • **Citric-phosphate buffer pH**: 6.8 • **Time intervals (min):** 30,45 & 60 • **Analyzed by:** UV spectrophotometric method at 286 nm

Table 3.2.1: In different dissolution medium Saturation Solubility of cervedilol.

Dissolution medium	Saturation Solubility (µg/mL)
citric-phosphate buffer + 0.1 % SLS	29.40
citric-phosphate buffer + 0.5% SLS	54.20
citric-phosphate buffer + 1% SLS	79.80
0.1 N HCl + 0.5% SLS	68.00
0.1 N HCl + 0.5% Tween 80	52.10
0.1 N HCl + 1% SLS	90.00
0.1 N HCl + 1% Tween 80	73.00
0.1 N HCl + 1.5% SLS	125.00
0.1 N HCl + 1.5% Tween 80	96.10
0.1 N HCl + 2% SLS	192.40
0.1 N HCl + 2% Tween 80	130.00
0.1 N HCl+ 2.5% SLS	285.00
0.1 N HCl + 2.5% Tween 80	181.00
0.1 N HCl + 3% SLS	370.00
0.1 N HCl + 3% Tween 80	245.00
Purified water + 0.5% SLS	96.75
Purified water + 0.5% Tween 80	60.20
Purified water +1% SLS	180.20
Purified water + 1% Tween 80	94.00

Table 3.2.1 (Continued) :

Dissolution medium	Saturation Solubility (µg/mL)
Purified water + 1.5% SLS	243.00
Purified water + 1.5% SLS	243.00
Purified water + 1.5% Tween 80	120.00
Purified water + 2% SLS	363.40
Purified water + 2% Tween 80	161.00
Purified water + 2% SLS	448.40
Purified water + 2.5% Tween 80	211.00
Purified water + 3% SLS	621.00
Purified water + 3% Tween 80	302.00

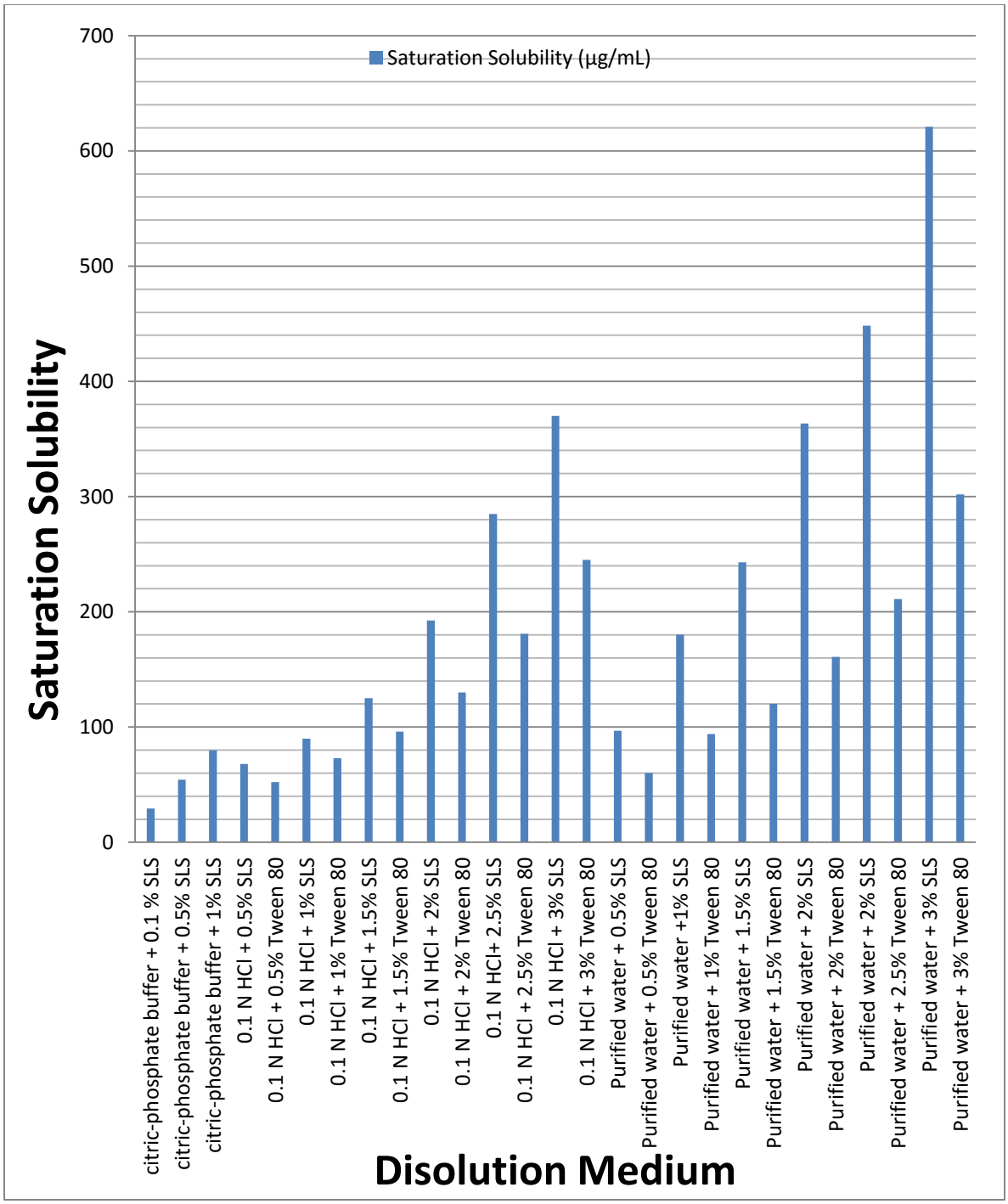


Figure 3.2.1: Saturation Solubility of cervedilol tablets in different dissolution medium

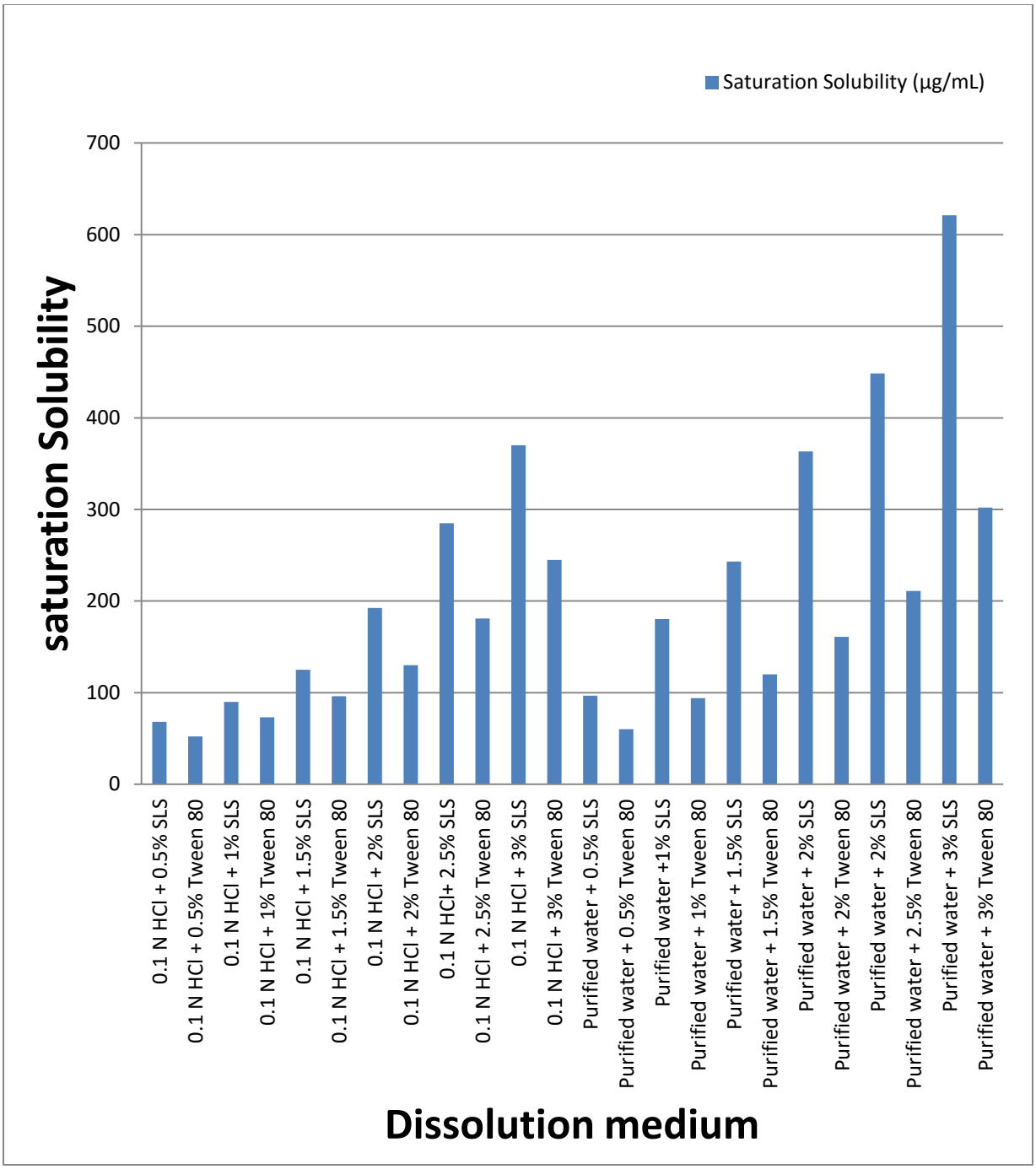


Figure 3.2.2: Saturation Solubility of cervedilol tablets in different dissolution medium (Comparison between SLS and Tween 80)

Carvedilol is a nonselective beta blocker/alpha-1 blocker utilized as a part of the treatment of mellow to extreme congestive heart failure (CHF) and hypertension. It has had a critical part in the treatment of congestive heart failure.

Solubility assumes a prime part in the dissolution of a drug substance from a solid dosage form. The solubility of carvedilol was determined at room temperature (28°±1°C) in different fluids (Table 3.2.1). The solubility was increased with the increase of the concentrations of surfactants.

Saturation solubility of carvedilol in different dissolution medium is shown in Table 3.2.1 Saturation solubility of carvedilol in citric-phosphate buffer, 0.1 N HCl & Purified water with SLS has shown (29.40-79.80) µg/mL, (68.00-370.00) µg/mL & (96.75-621.00) µg/mL respectively. For 0.1 N HCl & Purified water with Tween 80, saturation solubility has shown (52.10-245.00) µg/mL & (60.20-302.00) µg/mL respectively.

For poorly soluble drugs, surfactants are used to increase drug solubility (Wang et al., 2006).The FDA recommended the utilization of SLS in dissolution media for many lipophilic drugs. The solubility of carvedilol in purified water and 0.1 N HCl was increased in the presence of surfactants. The solubility was increased as the concentrations of surfactants were increased. Improvement in the solubility is more in case of SLS compared to Tween 80 solutions. Using 3% of SLS has been suggested for conducting dissolution tests for insoluble drug which results best solubility in 0.1 N HCl & Purified water.

In this study, 1.0 % w/v SLS in pH 6.8 citric-phosphate buffer medium results sink conditions. For that reason, 1.0% SLS was selected to improve the solubility of the drug in 6.8 citric-phosphate buffer.

Table 3.2.2: In different dissolution medium Percentage of drug release of cevedilol tablets.

Time	CT1 in DM 1	CT2 in DM 1	CT1 in DM 2	CT2 in DM 2
0	0	0	0	0
5	36.20	30.60	59.90	48.70
10	44.30	43.50	67.60	60.20
15	55.10	49.90	78.60	72.50
30	66.90	59.20	85.00	81.50
45	75.50	68.70	92.70	88.60
60	83.40	74.20	99.90	95.70

Note: **(Dissolution medium)**

DM1: 1 % sodium lauryl sulphate in 0.1 N HCL

DM2: 1% sodium lauryl sulphate in water

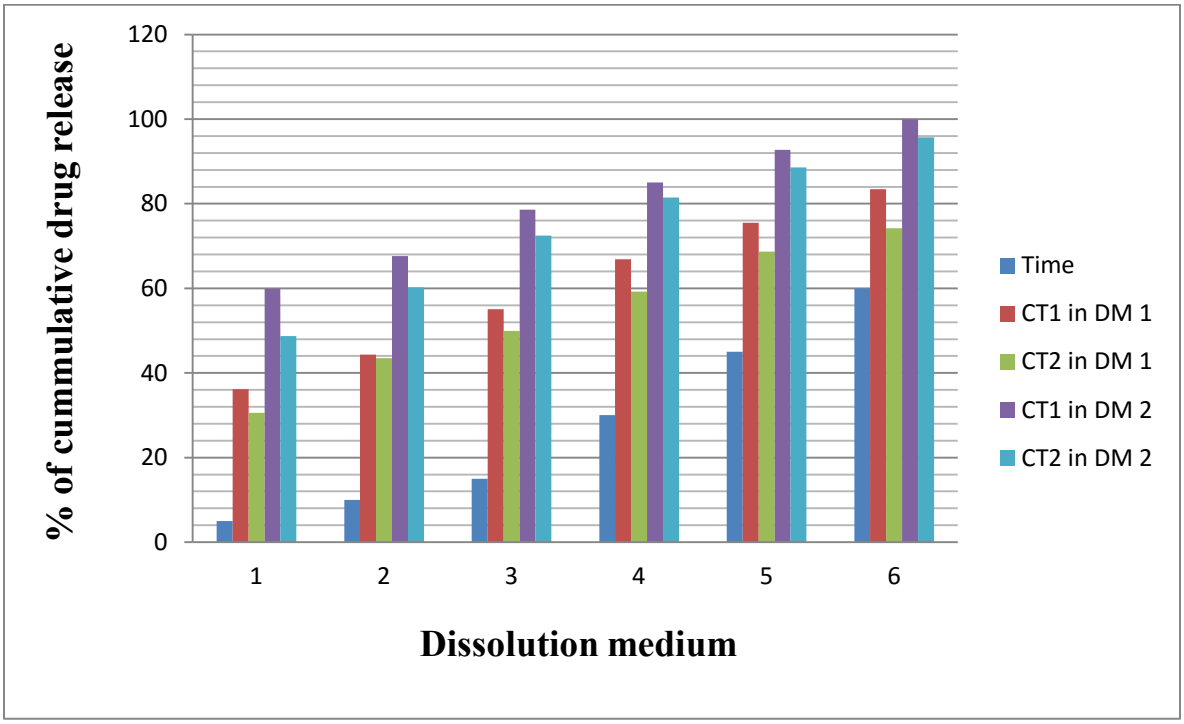


Figure 3.2.3: Percentage of drug release of Carvedilol tablets

Dissolution of carvedilol from two commercial formulations was studied in the above dissolution media. The dissolution of carvedilol from CT1 and CT2 in dissolution medium-2 was higher when compared to the dissolution of carvedilol in dissolution medium-1 (Table-3.2.2). The observed enhancement in the dissolution rate of commercial formulations observed because of high solubility of the drug in purified water compared to HCl containing SLS. The release from CT 1 was rapid and complete when compared to CT 2, which exhibited low dissolution initially which is shown in (figure 3.2.3).

The solubility of carvedilol in purified water and 0.1 N HCl has increased in the presence of surfactants. The solubility has increased with the concentrations of surfactants was increased.

3.3 Carbamazepine–Nicotinamide Co crystal

After reviewing the literatures worked on Carbamazepine–Nicotinamide Cocrystal we found that

3.3.1 For Carbamazepine–Nicotinamide Cocrystal: Article 1 (Li et al., 2013)

Material	Method
• Anhydrous carbamazepine (CBZ III) • Nicotinamide (NIC) • Tween 80 • Sodium lauryl sulfate (SLS) • Methanol (HPLC grade) • Double distilled water • Carbamazepine dihydrate (CBZ DH) • 1:1 carbamazepine–nicotinamide (CBZ–NIC) cocrystal	**Surfactant solutions**: • 0.35, 1.7, 3.5, 6.9, 10.4, 17.3, 34.7 mM SLS solutions and • 0.076,0.76, 1.5, 2.3, 3.8, 7.6, 17.3 mM Tween 80 solutions **Eutectic concentration measurements are done for determining solubility. The equation is** (Good, 2009): $S_{AB} = \sqrt{K_{sp}} = \sqrt{[A]_{eu}\,[B]_{eu}}$

Table 3.3: CBZ–NIC co crystal eutectic point, co crystal solubility and solubility ratio data.

Solvent	**concentration (mM)**	**[*CBZ*]eu (mM)**	**[*NIC*]eu (mM)**	**Cocrystal solubility *Scc* (mM)**	**Solubility ratio *Scc*/*SCBZ,aq***
Water		15.10 ± 1.32	1,956.80 ± 126.80	171.90	319
SLS	0.35	15.9 ± 1.80	1,665.20 ± 62.60	162.80	302
	1.70	16.30 ± 0.76	1,807.90 ± 90.30	171.50	319
	3.50	17.60 ± 0.63	1,818.90 ± 57.00	178.70	332
	6.70	17.50 ± 0.65	1,914.00 ± 136.30	183.20	340
	10.40	17.70 ± 0.42	1,811.10 ± 65.70	179.20	333
	17.30	18.10 ± 0.70	1,934.60 ± 51.80	187.30	348
	34.70	16.10 ± 2.77	1,839.50 ± 255.90	171.80	319

Table 3.3 (continued):

Tween 80	0.076	15.50 ± 0.68	1,847.30 ± 15.60	169.50	315
	0.76	15.90 ± 0.37	1,852.30 ± 56.90	171.70	319
	1.50	16.00 ± 0.70	2,024.30 ± 50.90	180.20	335
	2.30	17.40 ± 1.65	1,853.30 ± 109.90	179.50	334
	3.80	16.75 ± 2.78	1,624.50 ± 69.10	164.90	306
	7.60	14.98 ± 0.45	1,691.10 ± 87.40	159.20	296
	17.30	15.33 ± 0.89	1,638.90 ± 79.80	158.50	294

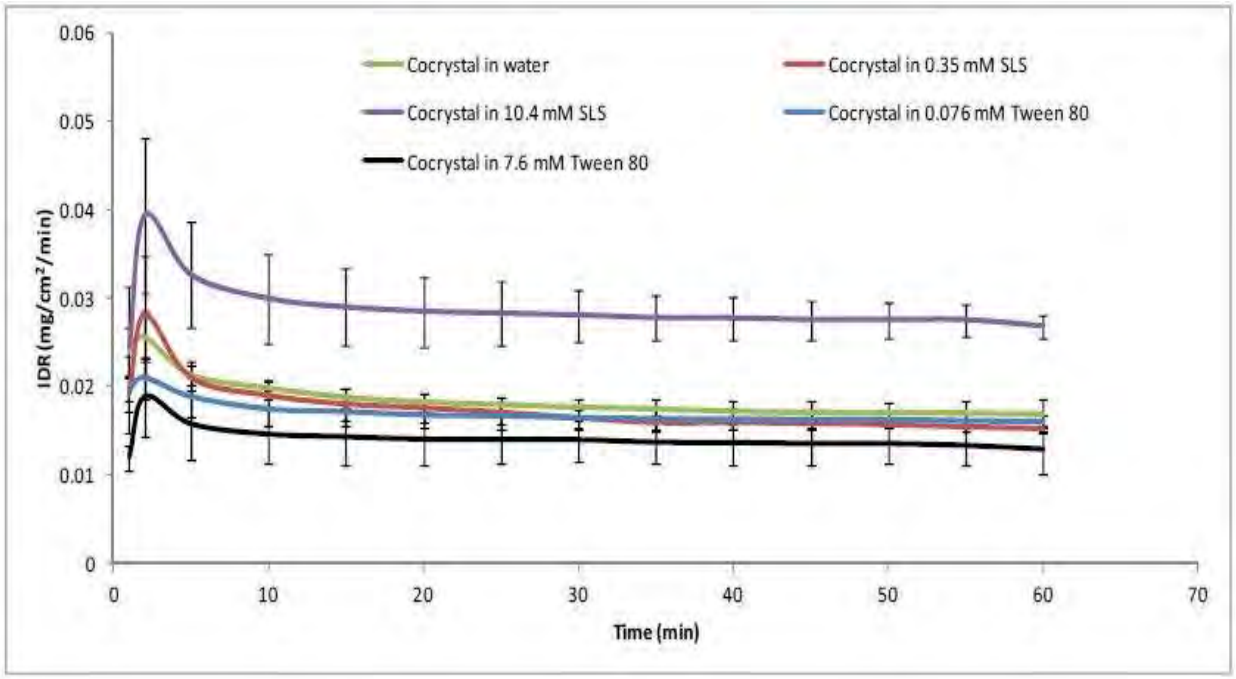


Figure 3.3.1(a): Test of dissolution profiles of samples at different dissolution media, CBZ–NIC cocrystal (Li et al., 2013).

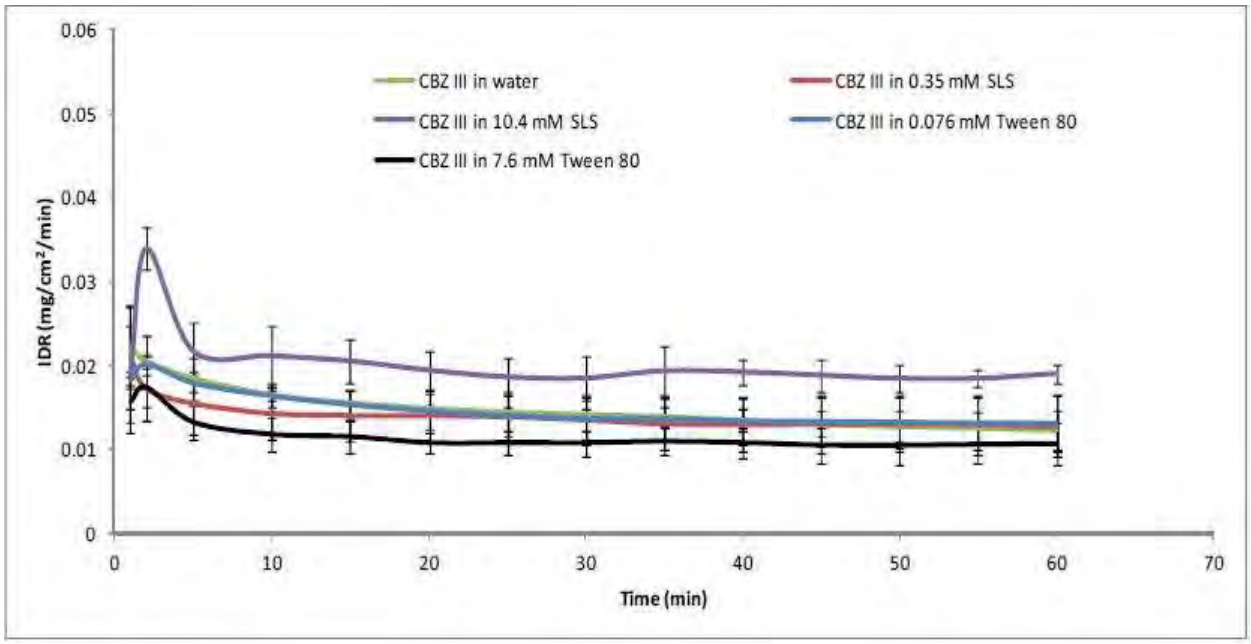


Figure 3.3.1(b): Test of dissolution profiles of samples at different dissolution media, CBZ III (Li et al., 2013).

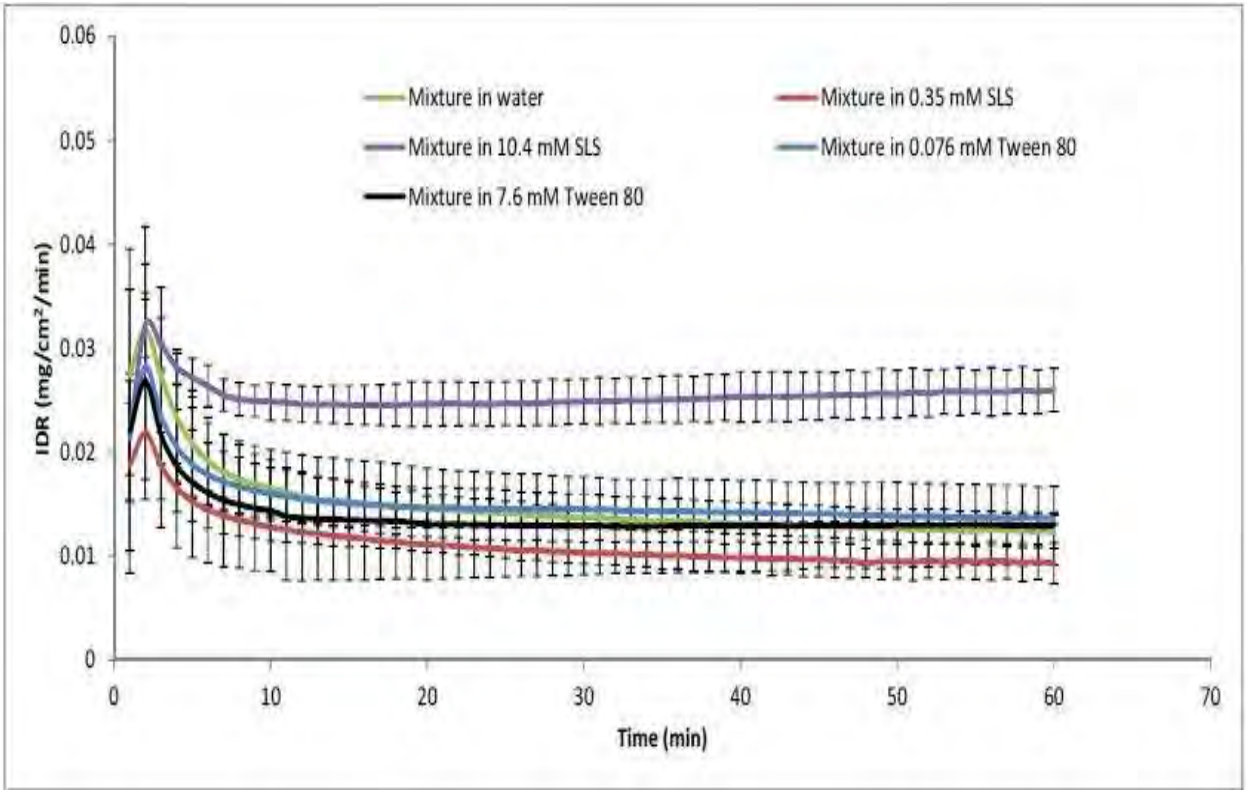
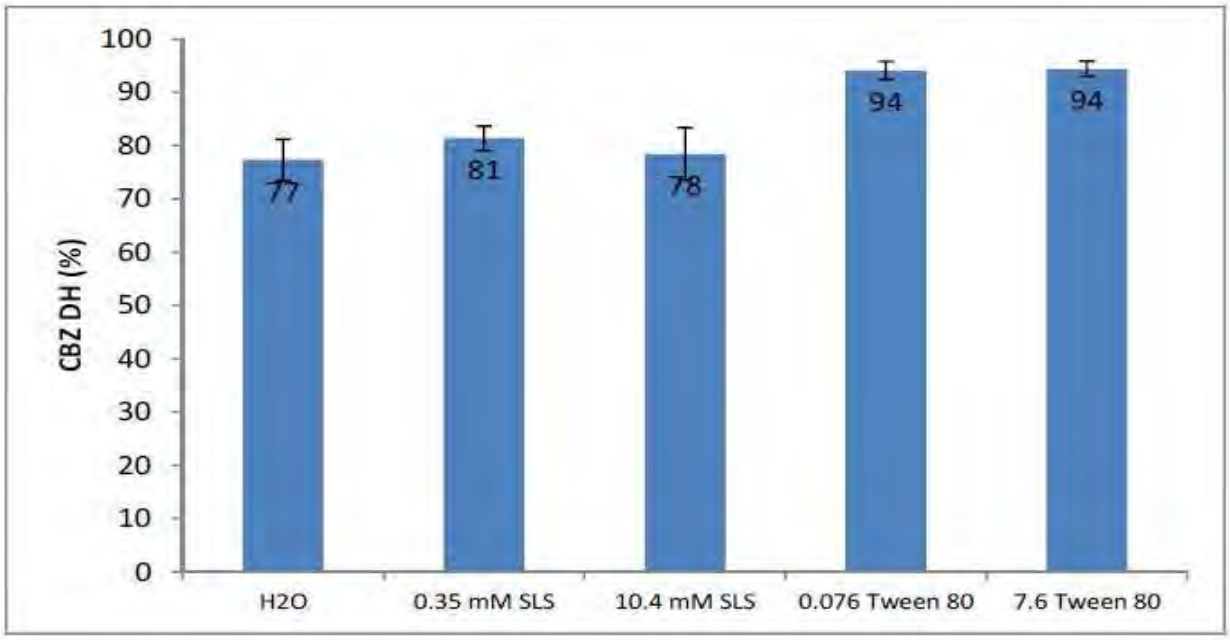
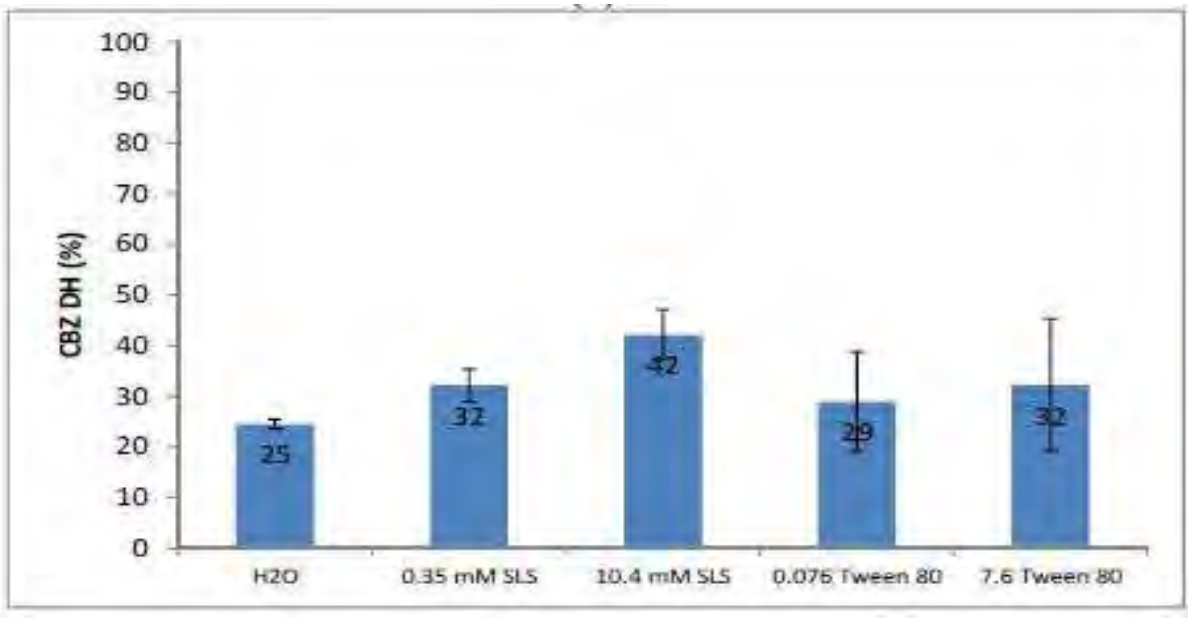


Figure 3.3.1(c): test of dissolution profiles of samples at different dissolution media, equimolar physical mixture of CBZ III and NIC (Li et al., 2013).



Figurer 3.3.2(a): Comparison of percentages of CBZ DH on the surfaces of sample compacts after dissolution test. CBZ–NIC co crystal (Li et al., 2013).



Figurer 3.3.2(b): Comparison of percentages of CBZ DH on the surfaces of sample compacts after dissolution test. CBZ III (Li et al., 2013).

It is surely understood that surfactants can improve dissolution of inadequately water-soluble drugs in two routes, either by bringing down the surface pressure at the solid drug surface to expand the surface zone accessible for dissolution or by increasing medication increasing (Chenet al., 2003)

$$S_{AB} = \sqrt{K_{sp}} = \sqrt{[A]_{eu}\,[B]_{eu}}$$

.

Where *K*sp is the co-crystal solubility manufactured goods and [*A*]eu and [*B*]eu are the eutectic concentrations of drug and conformer at equilibrium.

The solubility of the pure CBZ III, the CBZ–NIC co crystal and the physical mixtures of CBZ III and NIC was studied here.

Table 3.3 showed that the aggregate centralizations of CBZ and NIC at the eutectic purposes of diverse concentrations of SLS and Tween 80. Measuring the eutectic point in water, higher SLS concentration build the clear solubility of CBZ increased marginally. As per the solvency meaning of a 1:1 co crystal (as indicated by the above comparison), the solubility of the CBZ–NIC co crystal at diverse concentrations of SLS has shown in Table 3.3. The solubility of the CBZ–NIC co crystal was almost consistent and same as that in water when the SLS concentration was underneath its CMC and it expanded somewhat when the SLS focus was over its CMC.

The apparent solubility of CBZ was practically same contrasted and the eutectic point measured in water. While the concentration of NIC diminished at higher concentration of Tween 80 solutions, the clear solubility of CBZ was verging on consistent with an increment in Tween 80 concentration. The CBZ–NIC co crystal solubility was almost same as that in water at a lower concentration of Tween 80 solution and afterward diminished marginally when the Tween 80 concentration expanded (see Table 3.3).

The solubility of CBZ for has not expanded in 0.35 mM SLS dissolution medium under its CMC. Because of expanding rate of CBZ get dried out nucleation; the intrinsic dissolution rate profile of CBZ III in the 0.35 mM SLS dissolution medium was poorer than its comparing profile in water (Figure 3.3.1b). Since SLS does not impact CBZ DH nucleation for the dissolving CBZ–NIC cocrystal, the IDR profile of the CBZ–NIC cocrystal in the 0.35 mM SLS dissolution medium was practically comparable as its relating profile in water (Figure 3.3.1).

Dissolution investigations of the CBZ–NIC cocrystal with and without SLS demonstrate the same rate of CBZ DH encouraged on the surface of every example conservative (Figure 3.3.2a), showing that SLS does not encourage the surface-interceded nucleation of CBZ DH on the dissolving CBZ–NIC cocrystal. The rate of CBZ DH nucleation for the CBZ–NIC cocrystal dissolution was impacted for the most part by the co-previous NIC, as opposed to as an outcome of diminishing the interfacial pressure by SLS. Dissolution explores different avenues regarding CBZ III have demonstrated the expanded rates of CBZ DH encouraged on the surfaces of the example compacts with expanding surfactant concentrations of SLS and Tween 80 (Figure 3.3.2b), showed that both SLS and Tween 80 encouraged the surface-interceded nucleation of CBZ DH on the dissolving CB III.

3.4 Carbamazepine

After reviewing the literatures worked on Carbamazepine we found that

3.4.1 For Carbamazepine: Article 1 (John et al., 1997)

Material	Method
• Anhydrous Carbamazepine • 99% SLS & 95% SLS • CBZ dihydrate • Differential scanning calorimetry (DSC) • Thermogravimetric analysis (TGA) • Karl Fischer analysis machine • Distilled, deionized filtered water • The rotating machine • Model fitting • SYSTAT Statistics Software	**Dissolution Experiment:** • **Analyzed by:** Perkin Elmer Lambda 3B UV/VIS Spectrophotometer • **Time interval:** 2 minutes • **Rotational speed** : (50, 100, 200, and 300) rpm **Solubility Experiment:** • **Analyzed by:** Perkin Elmer Lambda 3B UV/VIS spectrophotometer at 285 nm.

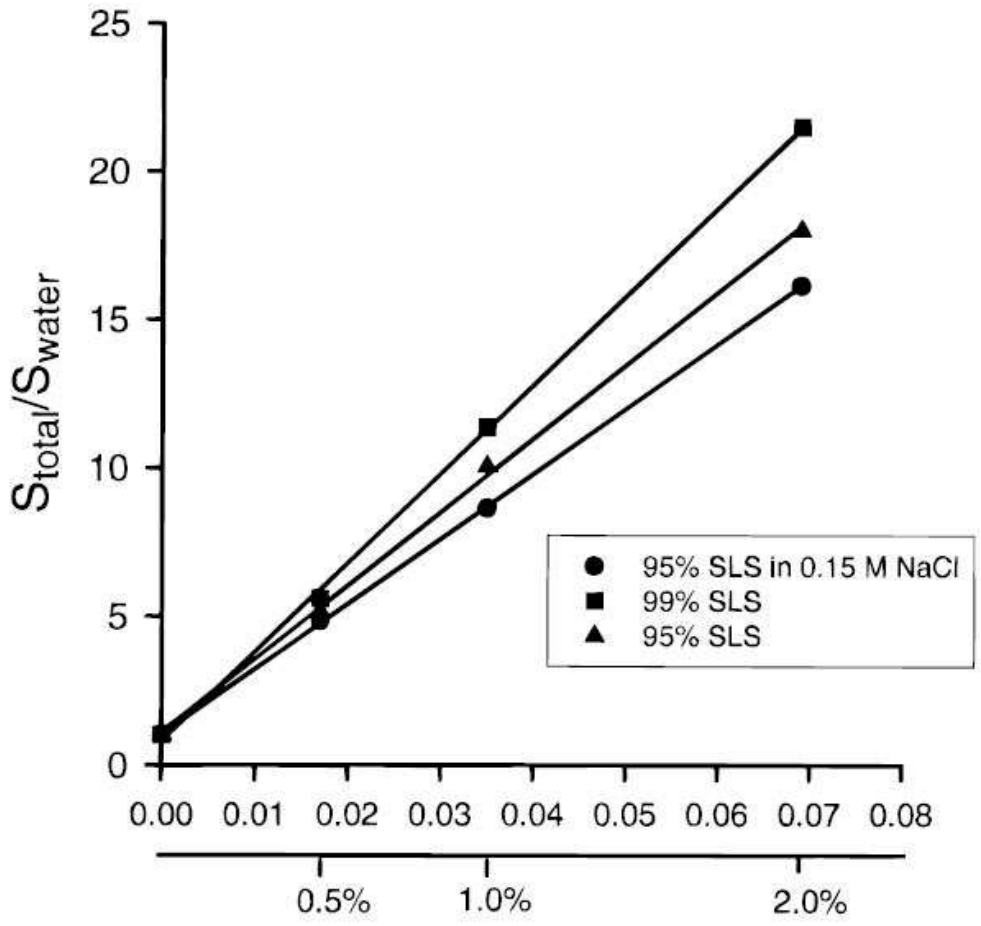


Figure 3.4: Solubility enhancement of CBZ in aqueous solutions of 99% SLS, 95% SLS, and 95% SLS with 0.15 M NaCl (John et al., 1997)

Here, S_{total} is the total solubility and S_{water} is the aqueous concentration of the solute.

$$\phi = \frac{J_{total}}{J_{solute}} = 1 + \frac{D_{sm}^{2/3}}{D_{s}^{2/3}} k^{*}[C_{m}]$$

This mathematical statement demonstrates that the flux improvement is a component of the diffusivity of the drug stacked micelle and the level of solubilization of the drug in the micelle (Higuchi, 1964).

The solubility improvement of CBZ in the 99% SLS, 95% SLS, and 95% SLS with 0.15 M NaCl solution has shown in the Figure 3.4. The equilibrium coefficients were dictated by regression analysis with the above mathematical statement and are 295, 265, and 233 L/M respectively. The differences in the solubility enhancement and equilibrium coefficient of CBZ in the three solutions are significant and may be due to competition between the solute and lauryl alcohol monomer for the micelle, closeness of packing between the monomers in the micelle as a result of charge screening from the electrolyte, or salting-out effects (Cochran, 1934; Brady, 1949; Preston, 1948).

For example, the repulsion between monomers due to the charge on the surfactant molecule may allow drug to be easily incorporated in the micelle. The presence of electrolytes, resulting in charge screening, may reduce this separation, thereby decreasing the solubility. In addition, surface-active impurities, such as lauryl alcohol, may lead to less space available for other molecules, resulting in a decrease in the solubility as observed.

3.5 Mefenamic acid:

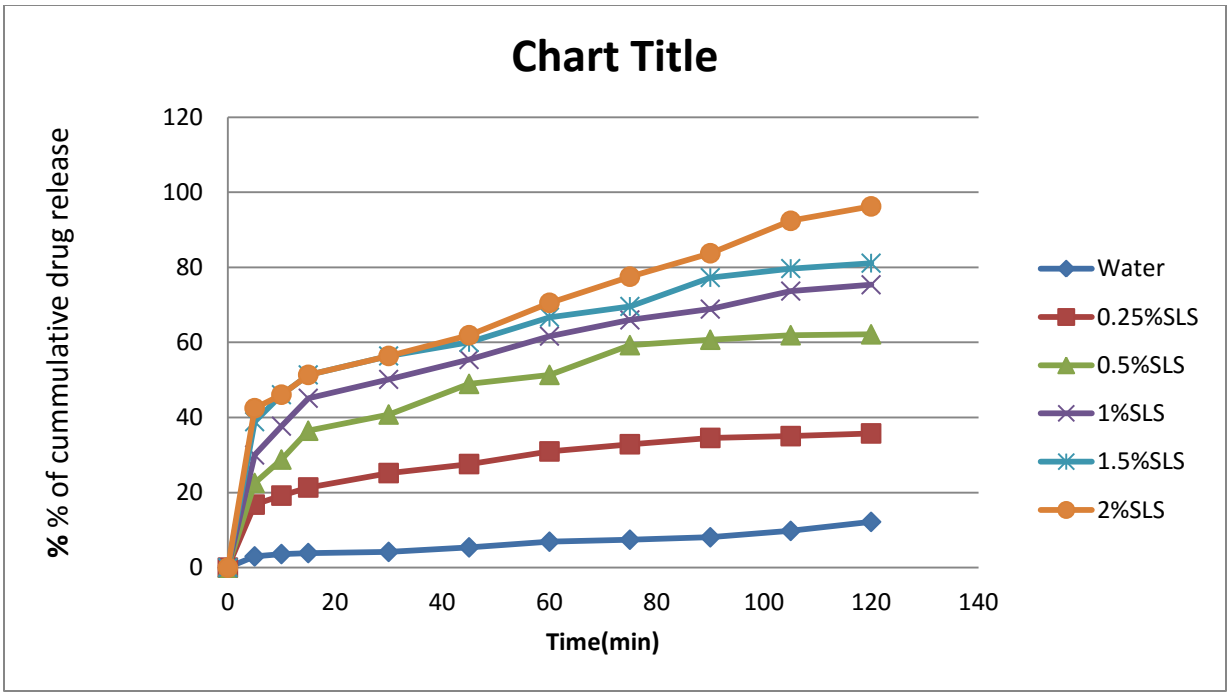
After reviewing the literatures worked on Mefenamic acid we found that

3.5.1 For Mefenamic acid: Article 1 (Patil et al., 2010)

Material	Method
• Mefenamic acid • Sodium lauryl sulphate • Tween 80 • Other chemicals	**Solubility study:** • **Temperature :** 37 ^{0}c • **Incubator maintained**: (37 ± 0.5) ^{0}c for 48hrs. • **Analyzed by**: Spectrophotometerically at 285 nm. **Dissolution study :** • **Apparatus :** USP dissolution apparatus II • **Temperature: (**37 ± 0.5) ^{0}c • **Rotational speed**: 50 rpm. • **Analyzed by**: Spectrophotometrically at 285 nm

Table 3.5: In different dissolution medium percentage of drug release of mefenamic acid.

Time (Min)	Water	0.25%SLS	0.5%SLS	1%SLS	1.5%SLS	2%SLS
0	0	0	0	0	0	0
5	3	**16.80**	22.56	30	38.88	42.48
10	3.624	19.20	28.80	37.68	46.08	46.08
15	3.888	21.36	36.48	45.12	51.36	51.36
30	4.20	25.20	40.80	50.16	56.40	56.40
45	5.40	27.60	48.96	55.44	60	61.92
60	6.912	30.96	51.36	61.68	66.72	70.56
75	7.44	32.88	59.28	66	69.60	77.52
90	8.088	34.56	60.72	68.88	77.28	83.76
105	9.792	35.04	61.92	73.68	79.68	92.40
120	12.192	35.76	62.16	75.36	81.12	**96.24**



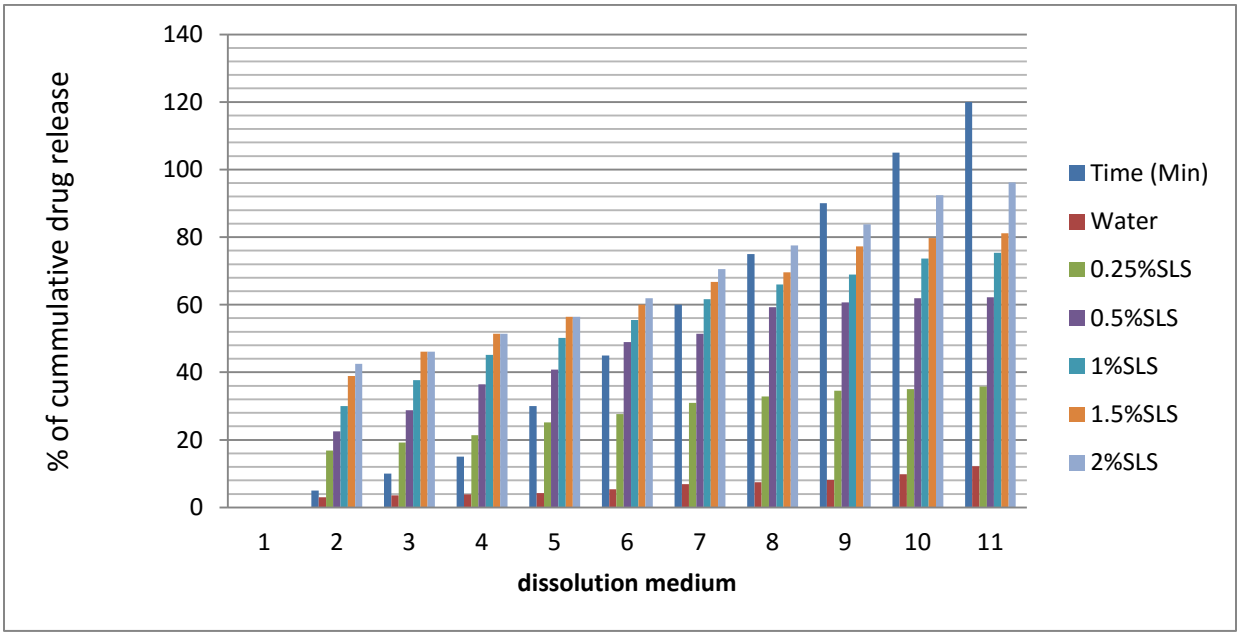


Figure 3.5: Percentage of drug release of Mefenamic acid

Mefenamic acid is water insoluble hence the solubility studies were carried out in different mediums. According to the data the solubility of Mefenamic acid is least in water and its solubility is maximum in water containing 2 % w/v of SLS and that is 96.24%.

The solubility of Mefenamic acid has increased with the increase of the pH of water. The solubility also increased on addition of surfactants. So, surfactants enhance the solubility of Mefenamic acid.

Among two surfactants, SLS has shown better result. That's why, water containing SLS has selected as dissolution medium. The solubility of Mefenamic acid in water containing various concentrations of SLS has been studiedin the article. Among all concentrations of SLS, the solubility of Mefenamic acid is more in water containing 2% w/v SLS.

Dissolution studies of Mefenamic acid capsules was carried out using water containing SLS as dissolution medium and the results were compared with dissolution profile of Mefenamic acid and inclusion complexes.

The improved dissolution profile of Mefenamic acid in surfactant containing SLS may be due to the fact the surfactants enhances the dissolution of pure drug by facilitating the drug release process at the solid/ liquid interface and micelle solubilisation in the bulk. (Schott et al. ,1982)

3.6 Simvastatin:

After reviewing the literatures worked on Simvaststin we found that

3.6.1 For Simvaststin: Article 1 (Fatima et al., 2014)

Material	Method
• Simvastatin • Sodium dihydrogen phosphate • Sodium hydroxide • Sodium lauryl sulphate • Distilled water	**Dissolution studies:** • **Dissolution apparatus:** USP dissolution apparatus 2 (paddle). • **SLS concentration in dissolution medium**: (0.1, 0.2, 0.3, 0.4 and 0.5) % • **Time interval**: (5, 10, 15, 30, 45 and 60) minutes • **Rotational speed**: 50 rpm • **Temperature**: (37 ± 0.5)°C • **Analyzed by**: UV vis Spectrophoto-metric method at 239 nm.

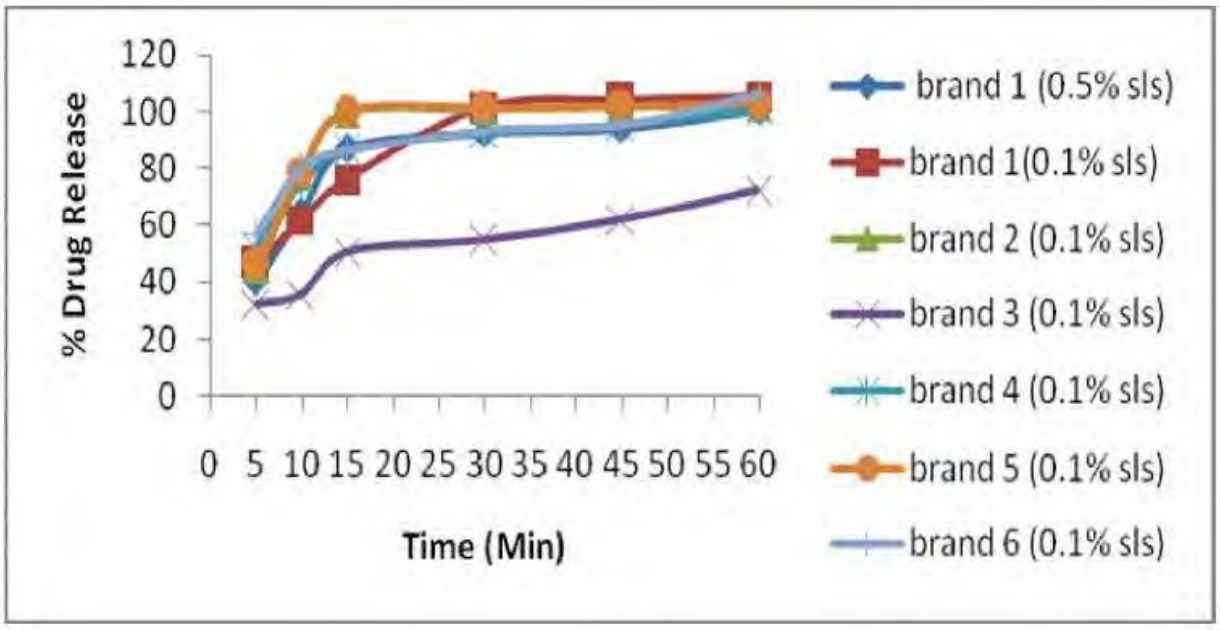


Figure 3.6.1 Percentage Drug release of brands in 0.1% and 0.5% SLS (Fatima et al., 2014).

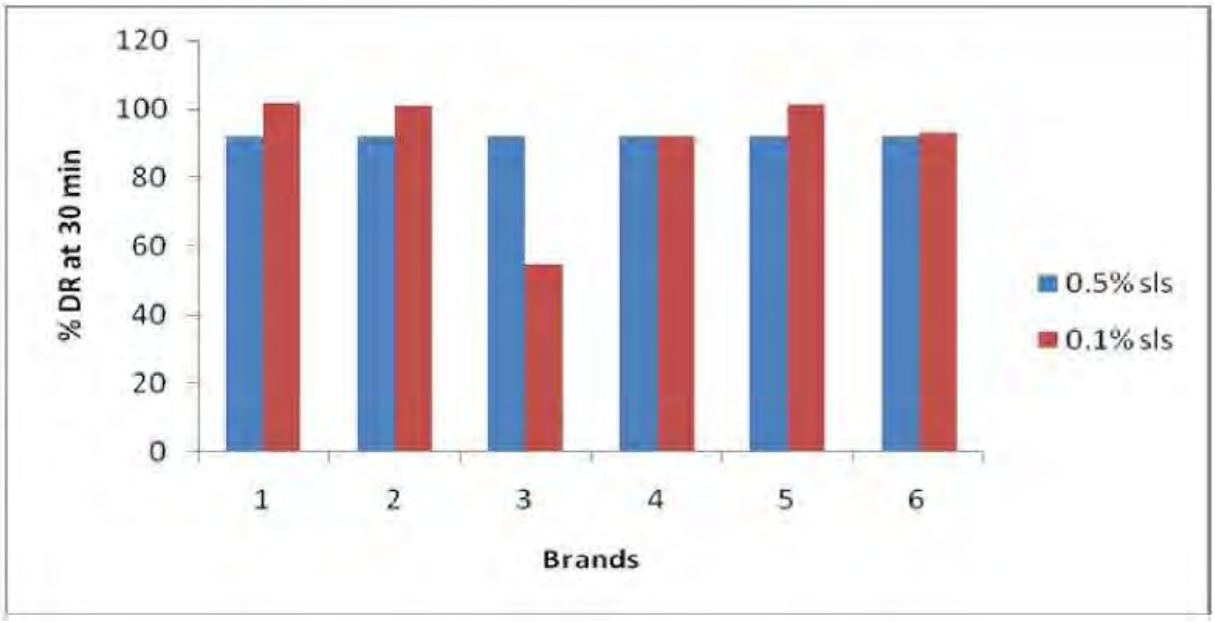


Figure 3.6.2 Comparison of % Drug Release at 30 minutes between 0.5% and 0.1% SLS (Fatima et al., 2014).

A dissolution test is a mean of identifying and proving the availability of active drug materials in their delivered form. A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form.

In the pharmaceutical industry, drug dissolution testing is regularly used to provide critical in vitro drug release information for both quality control purposes and to evaluate batch-to-batch consistency of solid oral dosage forms such as tablets and drug development, to calculate in vivo drug release profiles (Bai et al., 2011).

Simvastatin is a lipophilic compound with log p value 4.39 and its solubility is independent of pH of medium. For quality control dissolution test, an anionic surfactant such as SLS is recommended in a concentration of 0.5% in buffer (pH 7.0).

The aim of this study was to evaluate the effect of low concentrations of surfactant on the dissolution of poor soluble drug, Simvastatin tablets (20mg). Six brands were tested in different concentrations of SLS and percentage drug release were determined (Figure 3.6.1).

For quality control of Simvatatin, USP recommended pH 7.0 buffer with 0.5% SLS as dissolution medium. In this study all brands showed expected value in pH 7.0 with 0.1 % SLS (Figure 3.6.2) except one brand which failed to release even in 0.5%. The reason might be due to formulation parameters such as compression forces, hardness etc. Here 0.1% SLS act as discriminative biorelevant media for self emulsifying capsules higher concentration not closely relate the gastrointestinal solubility of drug (Singla et al., 2009).

3.7 Candesartan Cilexetil:

After reviewing the literatures worked on Candesartan Cilexetil we found that

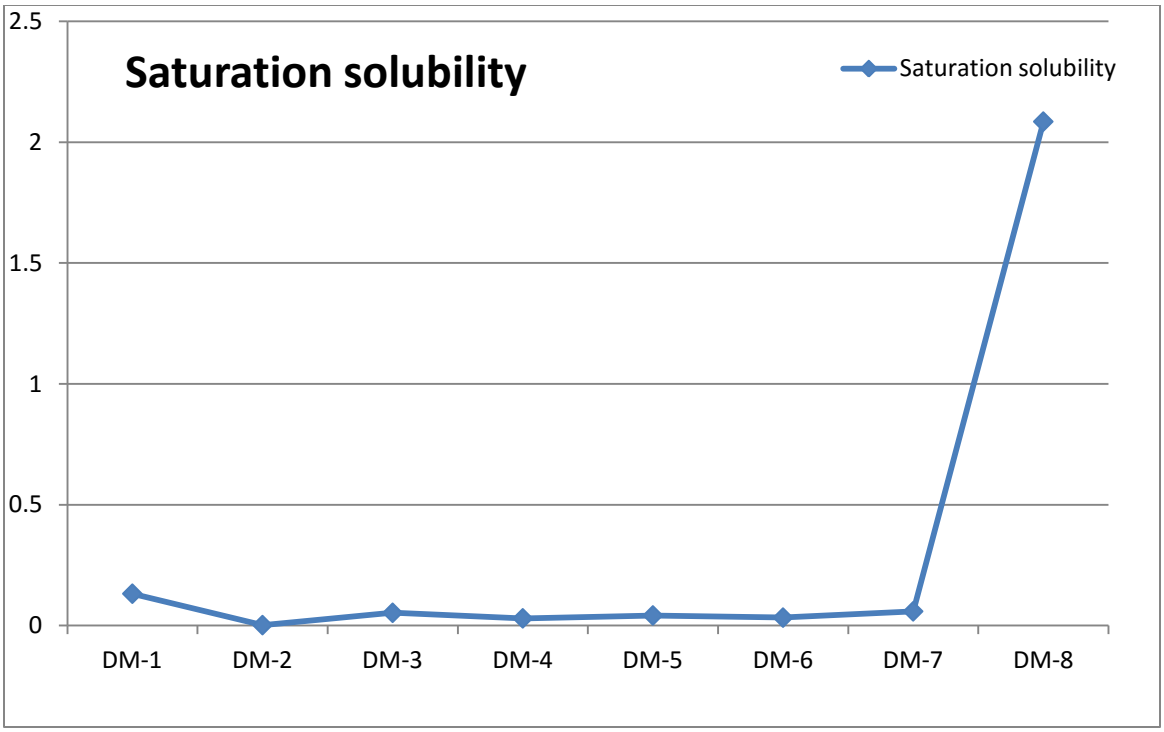
3.7.1 For Candesartan Cilexetil: Article 1 (Azim et al., 2012)

Material	Method
Instrument • USP Dissolution Apparatus II • HPLC instrument • UV/Visible detector • Electronic balance **Reagents and Solvents** • Potassium dihydrogen phosphate • Tween 20 • SLS • pH 4.5 acetate buffer • pH 2.0 buffer • pH 6.5 buffer • 0.1N HCl • Sodium hydroxide • Phosphoric acid • Hydrochloric acid • Acetonitrile	**Dissolution medium:** • 0.1% w/v SLS + 0.1N HCl. • 0.1% w/v SLS + pH 4.5 acetate buffer. • 0.35% w/v polysorbate 20 + phosphate buffer. • 0.25% w/v SLS + phosphate buffer. • 0.35% w/v SLS + phosphate buffer. • 0.35% w/v Tween 20 + phosphate buffer **Dissolution Parameters :** • **Medium**: Dissolution medium, 900 ml. • **Apparatus:** USP apparatus II (Paddle) • **Rotational speed:** 50 rpm • **Temperature: (**37 ± 0.05)^{0}c • **Time interval**: 15, 30 and 45 min.

SL no	Dissolution Medium
1	0.1N HCl+0.1% w/v SLS
2	pH 4.5 Acetate buffer +0.1% w/v SLS
3	pH 6.5 Phosphate buffer+0.1% w/v SLS
4	pH 6.5 Phosphate buffer+0.25% w/v SLS
5	pH 6.5 Phosphate buffer+0.35% w/v SLS
6	pH 6.5 Phosphate buffer+0.15% w/v Tween 20
7	pH 6.5 Phosphate buffer+0.25% w/v Tween 20
8	pH 6.5 Phosphate buffer+0.35% w/v Tween 20

Table 3.7: In different dissolution mediumsaturation solubility of Candesartan Cilexetil.

MEDIUM	DM-1	DM-2	DM-3	DM-4	DM-5	DM-6	DM-7	DM-8
Saturation solubility	0.132	0.002	0.053	0.03	0.042	0.033	0.059	2.085



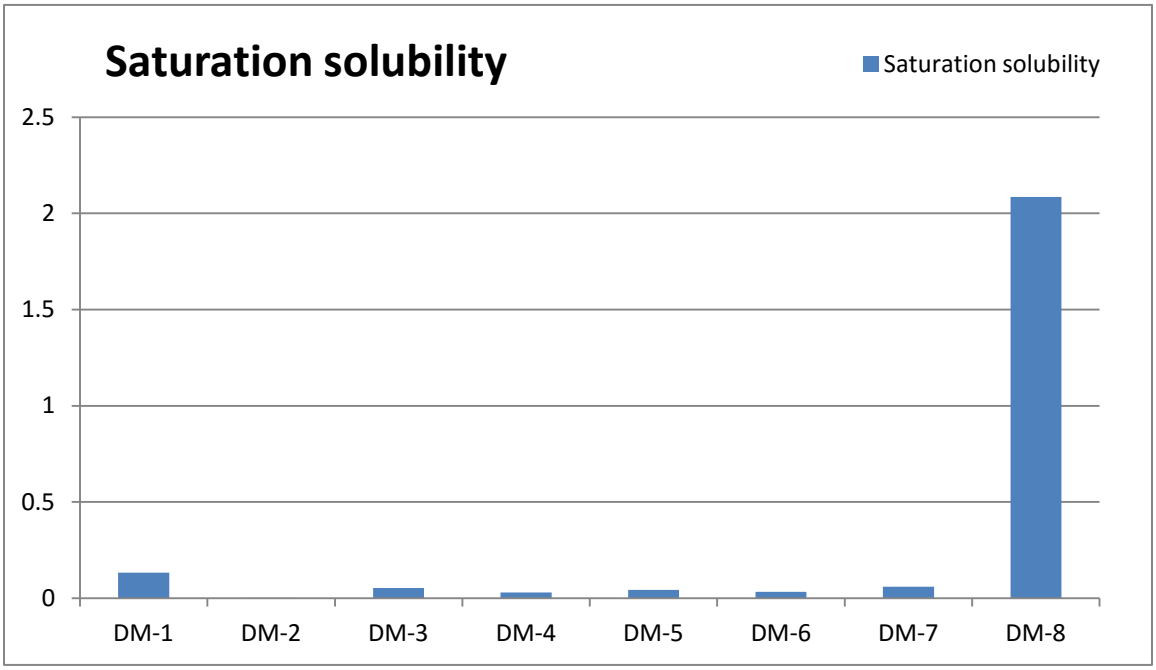


Figure 3.7: Percentage of drug release of Candesartan Cilexetil

The medium was selected on the basis of solubility data of Candesartan cilexetil in different dissolution medium at 37°C (Table 3.7). Drug release was carried out as per USP 2011 dissolution general specification at 50 rpm. All the buffers were made as per USP guidelines. The proposed dissolution was successfully applied for the better dissolution rate of Candesartan cilexetil in our body.

The data indicated that, for 0.25% w/v concentration of Tween 20 in Phosphate buffer pH 6.5 (DM 7) and concentration of surfactant of 0.35% w/v SLS in Phosphate buffer pH 6.5 (DM 5) showed incomplete drug release, where as complete drug release showed with Tween 20 at 0.35% w/v concentration (DM 8), (Figure 3.7). Therefore, the concentration of 0.35% w/v Tween 20 was selected for medium.

As 900 mL of pH 6.5 Phosphate buffer with 0.35% w/v Tween 20 satisfied the sink condition, it was considered to be a suitable dissolution medium. The result indicated that the dissolution rate of Candesartan cilexetil increased with increase in Tween 20 concentration in the dissolution medium. Thus, pH 6.5 Phosphate buffer with 0.35% w/v Tween 20 can be selected as a better dissolution medium, because this media shown the satisfactory % release of the drug. So, Tween 20 was preferred over SLS.

3.8 Ibuprofen:

After reviewing the literatures worked on Ibuprofen tablets we found that

3.8.1 For Ibuprofen tablets: Article 1 (Nighat et al., 2005)

Material	Method
• Cetyltrimethyl ammonium bromide (CTAB) • Sodium dodecyl sulphate(SDS) • Tween-80	**Dissolution study:** • **Dissolution apparatus**: USP Dissolution apparatus 1(basket) • **Temperature**: (37± 0.5)°C • **Rotational speed**: 100 rpm • **Time interval**: (10, 20, 30, 40, 50 and 60) minutes • **Blank solution**: Dissolution media • **Standard Solution**: 22.2 mg of Ibuprofen in 50 ml volumetric flask • **Analyzed by:** UV Visible spectrophoto-meter at 221 nm

3.8.2 For Ibuprofen tablets: Article 2 (Faruki et al., 2013)

Materials: Drugs and chemicals	Method
• Ibuprofen • Distilled water • Polyvinylpyrrolidone PVP K30 • Polyethylene Glycol PEG 6000 • Poloxamer • Sodium lauryl sulphate • Tween 80 • Mineral oil	**Dissolution study**: • **Dissolution apparatus**: USP Dissolution apparatus 1(basket) • **Rotational speed**: 50 rpm • **Temperature**: 37 ºC • **Measurement of Absorbance** : UV spectrophotometer at 214 nm • **Mesh size**: 40

SL No	Dissolution medium
DM 1	0.1%tween 80 + deionized water
DM 2	0.1%tween 80 + phosphate buffer PH 7.2
DM 3	0.01%tween 80 + deionized water
DM 4	0.01%tween 80 + phosphate buffer PH 7.2
DM 5	0.5% SDS + deionized water
DM 6	0.5% SDS + phosphate buffer PH 7.2
DM 7	0.1% SDS + deionized water
DM 8	0.1% SDS + phosphate buffer PH 7.2

Table 3.8: In different dissolution medium percentage of drug release of Ibuprofen.

Time	DM-1	DM-2	DM-3	DM-4	DM-5	DM-6	DM-7	DM-8
10	-43.69	-84.12	14.04	87.19	40.42	60.69	40.38	93.09
20	-43.69	-84.12	19.13	98.92	62.29	84.89	64.61	92.90
30	-43.69	-84.12	24.15	104.39	90.80	100.80	88.42	106.83
40	-43.69	-84.12	28.28	107.09	92.08	62.77	89.78	112.83
50	-43.69	-84.12	32.26	104.20	96.84	70.90	92.54	107.30
60	-43.69	-84.12	35.22	95.28	97.61	75.63	94.32	118.40

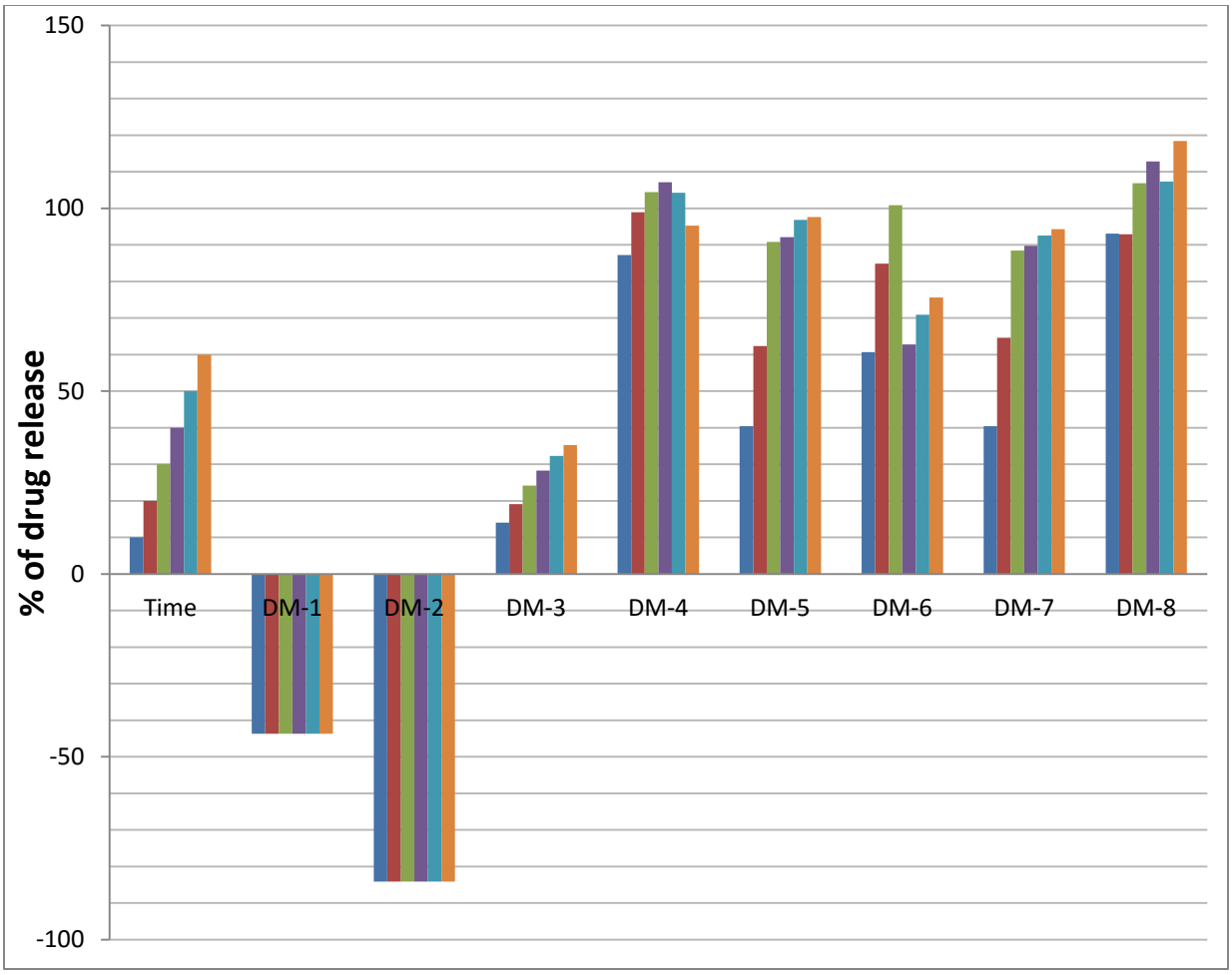


Figure 3.8: Percentage of Drug release of Ibuprofen

The dissolution rate of the drug was increased when anionic surface-active agent added in the de-ionized water, while moderate to good results were observed with the addition of cationic surfactant. Nonionic surfactant either showed retarding effect or very slight change in the dissolution rate when added in the water.

Table 3.8 indicated that the dissolution rate of the Ibuprofen tablets increased when the surfactant added in the de-ionized water, while their reduction or very little change in the dissolution when surfactant added in the buffer solution pH 7.2.

The dissolution rate of the drug increased when cationic surface-active agent added in the water at a concentration of 0.1 %. The rate was further increased as the concentration of the surface-active agent increased to 0.5%. This was due to the fact that the compound Ibuprofen was water insoluble and as the surface-active agent added in the system; it increased the wetting ability of the compound 'and thereby increased the solubility of the drug.

At a concentration of 0.1 % Tween-80 in dissolution medium, the results were found unsatisfactory and this was might be due the fact that at high concentration the dissolution media would become very viscous and did not allow the drug compound to dissolve in the dissolution media (Table 3.8).

In table 7 we saw that the dissolution medium 1 and dissolution medium 2 give the negative percentage of drug release after 10,20, 30, 40 ,50 and 60 minutes. Dissolution medium 1 and dissolution medium 2 gave the same percentage of drug released -43.69% and -84.12% respectively from 10minute to -60 minutes. That’s why those two dissolution medium should be negligible.

Chapter 4:

Conclusion:

Tablet Dissolution is a typical method for determining the rate of drug release from a dosage form. The principle purpose of the dissolution test may be the optimization of therapeutic efficacy during product development and stability assessment and also the bioequivalence study assessment along with the bioavailability study. One of the major difficulties facing the pharmaceutical industry now a day is to optimize the bioavailability as poor aqueous solubility impedes a drug's bioavailability and challenges its pharmaceutical development leading to ineffective treatment and at worst potentially hazardous due to a chance of toxic overdose. Drug release in the body can be determined in-vivo by measuring the plasma or urine concentrations in the subject concerned. However, there are certain obvious inconveniencies involved to employ such techniques. It is well known that use of surfactant can increase dissolution of poorly water soluble drugs in two different ways, i.e. either by lowering the surface tension or y increasing drug solubility. The surfactant sodium lauryl sulfate, sodium dodekyl sulfate, Tween 80 and Tweed 20 has the capability to facilitate the surface mediated nucleation thus dissolving the API.

These difficulties have commanded to the outline of official in-vitro tests which are now rigorously and broadly defined in the respective Pharmacopoeia. In case of BCS Class-II drugs which have high permeability but low solubility we face a different kind of problem to correlate in vivo-in vitro study. For that reason there are so many researches are going on for improving the drug solubility in case of dissolution study by adding surfactant into the media. In this review project we have reviewed different types of literature who discussed about the development of dissolution medium of poorly soluble drug (mainly BCS class 2 drugs) by using surfactants.

For the study we have seen and go through the journals about the drugs having low solubility like Glipizide, Carvedilol, Carbamazepine, Mefenamic acid, Simvaststin, Candesartan Cilexetil and Ibuprofen. For the improvement of their dissolution medium different types of surfactants like SLS (sodium loryl sulfate), tween 80, SDS (sodium dodekyl sulfate) are being used.

For Glipizide, saturation solubility for SLS in water, SLS in phosphate buffer, Tween 80 in water and hydroxy propyl methyl cellulose has shown (108.99-378.02) µg/mL, (158.32-468.27) µg/mL, (7.35-145.24) µg/mL and (32.90-42.02)) µg/mL respectively. The study has shown that the highest saturation solubility has shown in the medium containing 0.75 % SLS in phosphate buffer having pH 6.8 (468.27 µg/mL).

For carvedilol, saturation solubility in citric-phosphate buffer, 0.1 N HCl & purified water with SLS has shown (29.40-79.80) µg/mL, (68.00-370.00) µg/mL & 96.75-621.00) µg/mL respectively. For 0.1 N HCl & Purified water with Tween 80, saturation solubility has shown (52.10-245.00) µg/mL & (60.20-302.00) µg/mL respectively. Carvedilol shown good solubility in acidic medium (0.1 N HCl). Dissolution of carvedilol from two commercial formulations was studied in those two dissolution medium (1 % sodium lauryl sulphate in water and 1 % sodium lauryl sulphate in 0.1 N HCL). The dissolution rate of commercial formulations shown that high solubility in purified water compared to HCl containing SLS.

The solubility study of the pure CBZ III, the CBZ–NIC co crystal and the physical mixtures of CBZ III and NIC has shown that SLS, Tween 80 has been used in different concentration underneath its CMC. In case of increased amount of SLS in dissolution medium the release profile of CBZ-NIC increased significantly in comparison with that in water. The CBZ–NIC co crystal solubility was almost same as that in water at a lower concentration and afterward diminished marginally when the Tween 80 concentration increased.

For simvastatin six brands were tested in different concentrations of SLS and percentage drug release were determined. In this study all brands showed the expected value in pH 7.0 with 0.1 % SLS except one brand which failed to release even in 0.5%. The reason might be due to formulation parameters such as compression forces, hardness etc.

Mefenamic acid and Ibuprofen is also low water soluble drug. Hence the solubility studies were carried out in different mediums. For Mefenamic acid, percentage of drug release was shown maximum in water containing 2 % w/v of SLS (96.24%). For Ibuprofen maximum percentage of drug release was shown in 0.1% SDS + phosphate buffer PH 7.2.

For Candesartan Cilexetil, 0.25% w/v concentration of Tween 20 in Phosphate buffer pH 6.5, incomplete drug release has shown, where as complete drug release showed with Tween 20 at 0.35% w/v concentration. Therefore, the concentration of 0.35% w/v Tween 20 was selected for medium.

Finally we can come to a decision that most of the low less water soluble drug can be solubilize in a dissolution medium by using sodium lauryl sulphate of 0.75-3% and polysorbate 80 (Tween 80) of upto 0.5% along with other surfactant or alone depending on the solubility and nature of the drug. However to correlate the in-vivo and in-vitro dissolution specially for BCS class-II drugs which is the most challenging task for any pharmaceutical industry now a days can be improved by using the methods discussed in this paper. We are hoping that further research will be carried out to standardize the dissolution method for the in-vivo in-vitro correlation study.

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