Research Article CODEN: IJPRNK ISSN: 2277-8713
Nalla Sriraviteja, IJPRBS, 2013; Volume 2(5):182-203 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

EFFECT OF APPLICATION OF SOLUBILIZERS SUCH AS PVP K 30,PEG 400 AND TWEEN 80 ON THE ENHANCEMENTOFSOLUBILITY OF IBUPROFEN BY FACTORIAL DESIGN

NALLA SRIRAVITEJA, KODALIPAVAN KUMAR, BANDELA RAJU, KANUMURI MADHURI
Department of pharmacy, Vishwabharathi college of pharmaceutical sciences, Perecherla, Guntur, India.

Accepted Date: 24/09/2013; Published Date: 27/10/2013

Abstract: The present study is to evaluate the application of solubilizers such as PVP K 30,PEG 400 and Tween 80 for enhancing the solubility of Ibuprofen, a BCS class II drug.The individual and combined effects of PEG 400, PVP K 30 and Tween 80 on the solubility were evaluated in a 2^3 fractional study.In the 2^3 fractional study the three factors namely PEG 400(factor A), PVP K 30 (factor B) and Tween 80 (factor C), each at the two levels (0 and 2% concentration),were investigated for the individual and combined effects on the solubility of Ibuprofen. The results of solubility were analyzed as per analysis of variance (ANNOVA) of 2^3 factorial designs to find out the individual and combined effects of the three factors involved.

Keywords: solubility, solid dispersion, factorial design, ANOVA, pvp k-30, tween 80, PEG 4000.

PAPER-QR CODE

Corresponding Author: Mr. NALLA SRIRAVITEJA

Access Online On:

www.ijprbs.com

How to Cite This Article:

Nalla Sriraviteja, IJPRBS, 2013; Volume 2(5):182-203

INTRODUCTION[1][2][3]

BCS classification is developed for the immediate release(IR) dosage form with respect to solubility and permeability. It helps to estimate the solubility , dissolution, permeability, bioavailability of the drug.

According to BCS, drug substances are classified as :

Class I : High Solubility – High Permeability

Class II : Low Solubility – High Permeability

Class III: High Solubility – Low Permeability

Class IV: Low Solubility – Low Permeability.

It is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers viz.

Absorption number is the ratio of the mean residence time to mean absorption time.

Dissolution number is the ratio of mean residence time to mean dissolution time.

Dose number is the mass divided by the product of uptake volume (250 ml) and solubility of drug.

Class I :Drugs having a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step.

e.g. Metoprolol, Diltiazem, Verapamil, Propranolol.

Class II :Drugs having a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. In vitro- In vivo correlation (IVIVC) is usually excepted for class I and class II drugs.

e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedinpine.

Class III :Drugs were permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption.

e.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

Class IV: drugs which create lot of problems for effective oral administration. They are rarely developed and reach the market. These are the more challenging drug which are to formulated to dosage form.

Those compounds have a poor bioavailability because they are not well absorbed over the intestinal mucosa so a high variability is expected.

Factors effecting solubility:

Solubility is define as the ability of one substance to form a solution with another substance. Therapeutic efficacy of a drug depends upon the bioavailability the solubility of drug. Solubility is one of the important parameter to achieve desired concentration of drug in systemic

circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability.

Particle Size

As a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. [11]

Temperature

If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature. [16]

Polarity

Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. [11][15][16]

Polymorphs

The capacity of a substance to crystallize in more than one crystalline form is polymorphism. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities.[17][18]

Methods to increase the solubility

Techniques Of Solubility Enhancement

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are:

I. Physical Modifications

A. Particle size reduction:

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

a. Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improve the dissolution properties of the drug. The micronisation is used to increased surface area for dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does

not change the saturation solubility of the drug. [20]

b. Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. [11][21]

a) Homogenization:

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles. Three types of homogenizers are commonly used for particle size reduction are conventional homogenizers, sonicators, and high shear fluid processors.

b) Wet milling: Active drug in the presence of surfactant is defragmented by milling. Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.[9] [22]

B. Modification of the crystal habit

Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc.. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates.

Amorphous >Metastable polymorph >Stable polymorph

C. Drug dispersion in carriers

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs. The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state. The various methods of solid dispersion are[11]

1. Solvent Evaporation Method

Various proportions of drug and carrier were used, fine powder of both are mixed and dissolved into a organic solvent were both are miscible and stirr untill it is completely soluble and then evapourate the solvent . Temperatures used for solvent evaporation generally lie in the range 23-65^0 C.[7][8]

2. Melt-Solvent Method

Drug is dissolved in organic solvent and the solution is poured into the melt of mannitol or polyethylene glycol then it is evapourated untill the solvent dries up.[7][8]

3.Hot melt extrusion: Drug and the carrier are processed and made to fine powder and then melted and then homogenised and then made into desired form like pellets,flakes,tablets,capsules etc.by cooling it some drugs like thermolabile can also be used in this as the exposure to high temperatures is very less time.[7][8][9]

4. Co-grinding Method: Drug powder and the carrier throughly mixed for some time and the mixture is then transferred into instrument like ball mill and etc were size reduction takes place and then it is collected after certain time.[7][8]

5. Co-Precipitation Method (Co-Evaporates): carrier is dissolved in aqueous phase and drug in organic solvent. Then the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then heated and evaporated. [7][8]

6. Co-Precipitation with Supercritical Fluid: A supercritical fluid exists as a single fluid phase above its critical temperature and pressure. Carbon dioxide is currently the most commonly used supercritical fluid because of its low critical temperature of carbon dioxide makes it attractive for processing heat labile pharmaceuticals. Carbondioxide is used as an antisolvent for solute but as a solvent for organic solvent it involves the spraying of drug in organic solvent into continuous supercritical phase flowing concurrently.[7][8][9]

7. Spray Drying Method: Drug is mixed with the carrier and dissolved in a organic solvent by stirring and then allowed to spray dry by using nozzle type mini spray dryer due to high temperature the droplets before reaching the bottom the organic solvent evaporates and solid dispersion is formed.[7][8]

8. Dropping Solution Method: Drug is mixed with carrier and allowed to melt and then pipetted out and dropped on a cool surface it solidifies to round particles the size and shape depends on the nozzle size, viscosity, temperature and densities of the melt. [8][9]

9. Lyophilization Technique: Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. [7][8][9]

10. Gel Entrapment Technique: Carrier is dissolved in organic solvent to form a clear and transparent gel. Then drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved. [7][10]

D. Complexation

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

Inclusion complexes are formed by insertion of drug molecule into a cavity formed by the complexing agents. In this arrangement, non polar area of the drug molecule is excluded from water due to its insertion in the complexing agents. One requirement for the complexing agent in such system is that it has a non polar core and polar molecules are cyclodextrins, The cyclic oligomers of glucose are relatively soluble in water and have a cavities of large enough to accept non polar portions of many drug molecules of cyclodextrins can consists of 6, 7 and 8 sugar residues and are classified as α, β and γ respectively. Due to geometric considerations sreriod molecules lend themselves very well for inclusion into cyclodextrin complexes.[5][11]

E. Solubilization by surfactants:

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonioni. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.[12]

Other methods to increase solubility

1.pH adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer

capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines.

Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds.11-14Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility

of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.[11][13]

2. Cosolvency:

This is technique to improve the solubility of poorly water soluble drugs, the addition of the organic solvent to water will leads to change in the polarity of the water molecules by reducing the interfacial tension and prevents the self association of water by preventing and interfering with the interhydrogen bonding of water molecules and will reduce the bonding of water molecules and increase the interaction with the hydrophobic solute, the solvent which is responsible for increase in the solubility is called as cosolvent and phenomenon is called as cosolvency. [11] [13][23][24]

3. Hydrotrophy:

Large amount of additives are added which will form the weak hydrotrophic interactions and increase the solubility.[11]

Example: Solubilisation of Theophylline with sodium acetate and sodium alginate

4.Precipitation Techniques:

Drug is dissolved in solvent and then added to non solvent then the drug will precipitate out as crystal which is controlled by the addition of surfactant.The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent.

Ex: Nanosuspension of Danazol, Naproxen prepared by precipitation technique to improve their dissolution rate and oral bioavailability.[4][6]

5.Cryogenic Techniques

It is the process of formation of nanoparticulate structures which are porous and increase the solubility of the drug which was done at low temperature conditions.[4][6]

6.Nanotechnology approaches:

Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and the next step taken was Nanonisation.[25][26][27]

Nanocrystal

A nanocrystal is a crystalline material with dimensions measured in nanometers; a nanoparticle with a structure that is mostly crystalline. The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 nanometers.

Nanocrystallization is thought to be a universal method that can be applied to any drug.

There are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components

S.NO:	Method	Examples of drugs
1	Buffering the PH of the micro environment	Bufferedaspirin,theophylline, sulfamethoxazole and cotrimoxazole sodium & potassium salts of pencillin V
2	Use of the salts of weak acids and weak bases	Sodium,potassium calcium salts of P-amino salicylic acid, sodium tolbutamide and Tetracycline.HCl
3	Use of solvates and hydrates	Ampicillin anhydride
4	Use of selected polymorphic form	Novbiocin,chloremphenicolpalmitate and succinylsulphothiazole
5	Complexation	Benzocaine-caffeine,digitoxin-hydroquinone,caffeine-ergot alkaloides
6	Prodrug approach	pivampicillin,Hectacillin,erythromycin-2^{I}-N-alkylsuccinate,2^{I}-N-alkylglutaramate, prodrugs of carbencillin,lincomycin and clindamycin
7	Use of surfactants	Hydrocortison-Tween 80,Amphotericin-B-biosurfactants(sod.taurocholate and sod.Cholate),tolbutamide-Tween 20 and Tween 80,sulphathiazole,prednisolone and chloramphenicol – poloysorbate 80

I) Methods which increase the surface area

1	**Micronization(particle size reduction to increase the surface area)**	**Griseofulvin,Digoxin,Phenacetin and Sulphadiazine**
2	Use of surfactants(To increase the effective	Phenacetin,Ethinamate and sulfisoxazole

	surface area by facilitating proper wetting)	
3	Solvent deposition(deposition of poorly soluble drugs on inerty material)	Oxyphenbutazone,prednislone,Tolbutamide,indomethacin and phenylbutazone
4	Solid disperssion	Griseofulvin-PVP,Reserpine-PVP,Tolbutamide-PEG,Chloremphenicol-urea

FACTORIAL STUDIES:

Factor: It is an assigned variable which can be qualitative or quantitative the choice of experiment depends on experimental objectives and its predetermined by the experiment. a quantitative factor has a numerical value assigned to it and qualitative factor assigned by name rather than numbers.[35]

Level: levels are the values or designations assigned to the factor. The runs or trails that comprise factorial experiments consists of all combinations of all levels of all factors.[35]

Effects: effect of factor is the change in response caused by varying the levels of a factor.

Interaction: lack of additivity is called as interaction, if two factors have an equal effect then when combined gives an effect more than expected then said to be synergistic if combined gives an less effect than desired it is called interaction.[35]

Advantages:

1) To identify the interaction and reason for interaction.
2) If there is no interaction, it has maximum efficacy in estimating main effects.
3) Maximum use is made of the data since all the main effects and interactions are calculated.
4) Factorial studies are orthogonal all estimated effects and interactions are independent of effects of other factors.[35]

In factorial experiments as the adjective factorial indicates the effects of several factors of variation are studied and investigated simultaneously, the treatments being all the combinations of different factors under study. In these experiments an attempt is made to estimate the effects of each of the factors and also the interaction effects i.e., the variation in the effect of one factor as a result to different levels of other factors.

an experiment with n factor, each at s levels where n is any positive integer greater than or equal to 2, e.g. 2^3 experiment with 3 factors at 2 levels each 3 experiment means an experiment with 2 factors at 3 levels each .

2^2Design:

Here we have two factors each at 2 levels(0,1) say ,so that there are 2 x 2 = 4

Treatment combinations in all. Following the notations due to Yeates,let the capital letters A and B indicate the names of the two factors undert study and let the small letters a and b denote one of the two levels of each of the corresponding factors and this will be called the second level . The frist level of A and B is generally expressed by the absence of the corresponding letter in the treatment combinations . The four treatements can be enumerated as follows :

$a_0 b_0$ or "1": factors A and B , both at frist level.

a_1 b_0 or a: A at second level and B at frist level

a_0 b_1 or b:Aatfrist level and B at second level

a_1b_1 or ab:Aand B both at second level

These four treatment combinations can be compared by laying out the experiment in (i)

R .B.D. , with replicates (say), each replicate contaning 4 units, or (ii) 4 x4 L.S.T., ANOVA can be carried out accordingly. In the above cases there are 3 d.f. Associated with the treatment effects . In factorial experiment our main objective is to carry out separate tests for the main effects A,B and the interaction AB , splitting the treatment S.S. With 3d .f into three orthogonal components each with 1 d.f. And associated either with the main effects A and B or the intersection AB.[38][39][40]

Main Effects and interaction :

Suppose the factorial experiment with 2^2=4 treatment is conducted in r-blocks or replicates as they are often called .let {1},{a}. {b} and {ab} denote the total yields of the r-units {piots} reciving the treatment 1, a, b, and ab respectively and let the corresponding mean values obtained on dividing these totals by r be denoted by {1},{a},{b},and{ab} respectively. The letters A,B and AB when they refer to numbers will represent the main effects due to the factors A and Band their interaction AB respectively. The effect of factor A can be represented by the difference between mean yields obtained at each level.

Thus the effects of factor A at the first b_0 of B

$= \{a_1b_1\}—\{a_0b_0\}$

$= (a)-(1)$ .... (5.1)

Similarly, the effect of at the second level b1 of B

$= (a_1b_1)-(a_0b_1)$

$=(ab)-(b)$ ....(5.1a)

These two effects in (5.1)and(5.1a) are termed as the simple effects of the factor A

The average observed effect of A over the 2 levels of B is called the main effect due to A and is identified by

A=1/2 [(ab)–(b)+(a)-(1)] : (5.2)

A simplified form of this is

A=1/2(a-1)(b+1)

Where the right hand side is to be expanded algebraically and then treatment combinations are to be replaced by treatment means

Arguing similarly we shall get main effect due to factor B as

B=1/2[(ab)-(a)+(b)-(1)] ...(5.3)

B =1/2(a+1)(b-1) ...(5.3a)

Where, again, the right hand is to be expanded algebraically and the treatment combinations are to be replaced by their treatment means

The interaction of 2 factors is the failure of the level of 1 factor say. A to retain the same order and magnitude of performance through out all level of the second factor, say ,B. if the two factors act independently of one another , we should expect the true effect of one to be same at either level of other . In other words we should expect that the 2 expression observed in (5.1) and (5.1a) were really the estimate the same thing. one the other hand, if the 2 factors are not independent the 2 expressions in (5.1) and(5.1a) will not be same and difference of these 2 numbers is, therefore a measure of the extent to which the factors interact and we write the 2 factor interaction are the first order interaction between the factors A&B as

AB=1/2[(ab)-(b)-(a)+(1)] ...(5.4)

(or)

AB=(a-1)(b-1) .....(5.4a)

Where, as usual R.H.S. is to expanded algebraically and the treatment combinations are to be replaced by corresponding treatment means.

Statistical analysis of 2^2 design:[38][39][40]

Factorial experiment are conducted either in C .R.D or R.B.D.or L.S.D. and thus they can be analyzed in the usual manner except that in this case the treatment S.S is split in to three orthogonal components each with one d.f. it has already been appointed out that the main effect A&B , and the interactions AB are mutually orthogonal contrasts of treatment means the S.S due to the factorial effects A,B&AB is obtained by , multiplying the squares of the factorial effect by suitable quantity in practice these effect usually computed from the treatment totals (a) ,(b) , (ab) etc.. rather than from the treatment means (a),(b) etc.. factorial effect totals are given by the below expressions

[A]=[ab]-[b]+[a]-[1]

[b]=[ab]+[b]-[a]-[1]

[AB]=[ab]-[a]-[b]+[1]..... (5.5)

The S.S due to any factorial effect obtained on multiplying the square of the effect total by the factor (1/4r) , where r is the common replication number (c ,f , remark below) thus ,

S.S due to main effect of A = [A] 2/4r

S.S due to main effect of B=[B]2/4r

And S.S due to interaction AB=[AB]2/4r....(5.6) each with 1 d.f

2^3 factorial experiments: In 2^3 experiment consider 3 factors say, A,B&C each at 2 levels , say, (a_0,a_1), (b_0,b_1) and ,(c_0,c_1) respectively , sp that there are 2^3 =8 treatment combinations in all. Extending the notations due to Y ates for a 2^2 – experiment, at the corresponding small letters a,b&c denote the second level of the each of the corresponding factors . The first level of each factor A, B, &C is signified by the absence of corresponding letter in the treatment combinations, the 8 treatment combinations in a standard order are

'1' , a, b, ab, c ,ac ,bc, ,abc, where for example

1= $a_0b_0c_0$, a= $a_1b_0c_0$, ab=$a_1b_1c_0$,abc=$a_1b_1c_1$ etc..

2^3- factorial experiment can be performed as a C.R.D. with 8 treatments , or R.B.D . with r replicated (say) , each replicate containing 8 treatments or L.S.D with n=8 and data can be analysed accordingly . In 2^3 experiment we split up the treatment S.S with 7 d.f. in to seven orthogonal components corresponding to the three main effect A.B.&C, 3 first order(or 2 factor) interactions AB,AC,&BC and one second order interaction(or 3 factor interaction) ABC, each carrying 1.d.f. as in the case of 2^2 experiment A, B ,AB,BC etc. when they refer to numbers represent the corresponding factorial effects.[38][39][40]

POLYSORBATE 80(TWEEN 80)

Nonionic surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid. Polysorbate 80 is a viscous, water-soluble yellow liquid. Density1.06-1.09 g/mL, oily liquidBoilingpoint>100°C Very soluble inwaterSolubility in other solvents soluble in ethanol, cottonseed oil, corn oil, ethyl acetate, methanol, toluene. The critical micelle concentration of polysorbate 80 in pure water is reported as 0.012 mM.[33]

PEG 400 (polyethylene glycol 400)

Is a low-molecular-weight grade of polyethylene glycol. It is a clear, colourless, viscous liquid. soluble in water,acetone,benzene,glycerine,density1. 110-1.140 Due in part to its low toxicity, PEG 400 is widely used in a variety of pharmaceutical formulations.[33]

PVP K 30

Binder disintegrate, dissolution aid, suspending agent Soluble in water ,freely soluble in chloroform, ethanol and acids Density is 1.180 gm[33]

METHOD USED FOR ESTIMATION OF IBUPROFEN

A spectrophotometric method based on the measurement of absorption at 221nm is phosphate buffer PH 7.2 was used in the present study of estimation of ibuprofen

Materials:

- Ibuprofen
- Methanol
- Potassium dihydrogen phosphate
- NaOH

Preparation of ph 7.2 phosphate buffer :

Take 6.8 gm of potassium di hydrogen phosphate dissolved in 1.388 gm of NaOH& make up to volume 1 liter

Stock solution-I:

50mg of ibuprofen dissolved in 25 ml of methanol in 50 ml of volumetric flask and the solution was made up to the volume with methanol.

Procedure:

The stock Solution-I of was subsequently diluted with phosphate buffer PH 7.2 to obtain the series of dilutions containing 2,4,6,8 and 10µg/ml. The absorbance of these solution was measured in ELICO-SL 159,U.V is the spectrophotometer at 221nm using phosphate buffer PH 7.2 as blank. The concentration of corresponding absorbance is given in table .The absorbance was plotted against concentration as shown in fig:2

Table 2:Absorbance readings:

S.NO	CONCENTRATION (µg/ml)	ABSORBENCE(n=4)
1	2	0.143 ± 0.09
2	4	0.271 ± 0.04
3	6	0.433 ± 0.07
4	8	0.585 ± 0.05
	10	0.742 ± 0.05

GRAPH

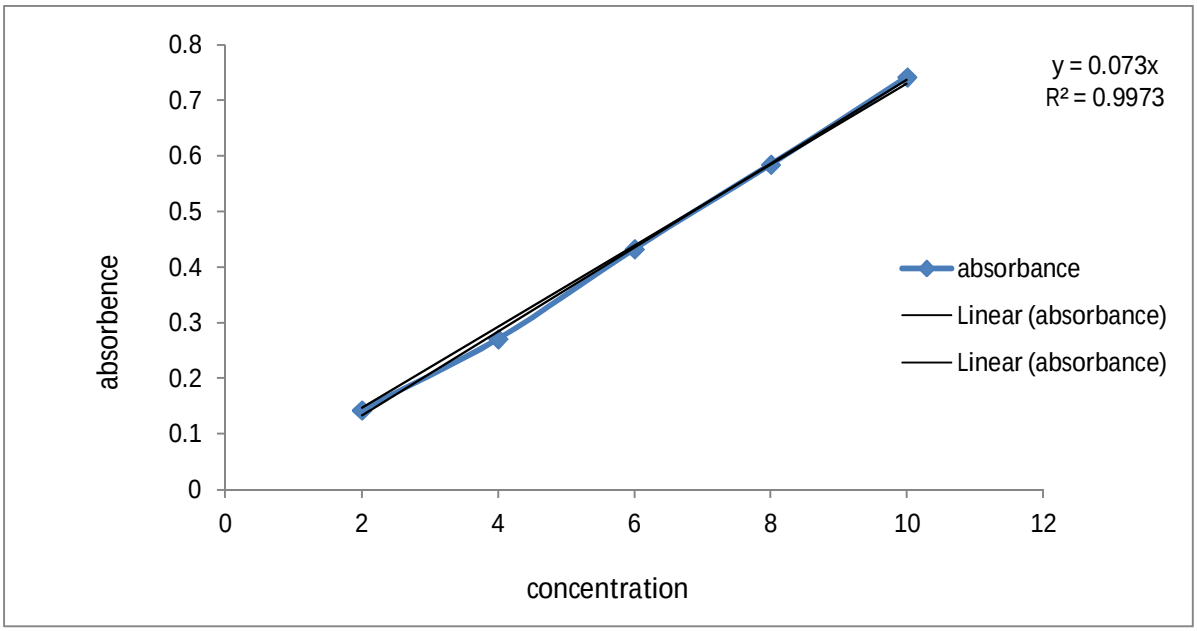

FIGURE:1 Calibration Curve

SOUBILITY DETERMINATION:

50 mg of drug added to 15 ml of each fluid in 25 ml stoppered conical flask, shaken for 10 hrs at room temperature in rotary flask shaker.

After 10 hr 2 ml of aliquot is withdrawn at 2 hrs interval, filter using fine 0.45 µ disk filter and dilutes suitably, assayed and measure the absorbance at 221snm.

NOTE: Solubility experiments are repeated for 4 times

Table: 3 Solubility data

S:no	contents	absorbance	Dilution factor	Concentration/solubility
1	Water	0.750	10	0.105
2	Water+2% PEG 400	0.243	1000	3.380
3	Water+2% PVP K30	0.291	1000	4.035
4	Water+2% + PEG 400+ 2% PVP K30	0.112	1000	1.560
5	Water+2% Tween 80	0.616	1000	8.540

6	Water+2% PEG 400+2% Tween 80	0.150	1000	2.09
7	Water+ 2% PVP K 30+ 2% Tween 80	0.202	1000	2.80
8	Water+ 2%PEG 400+ 2%PVP K30+ 2%Tween 80	0.185	1000	2.57

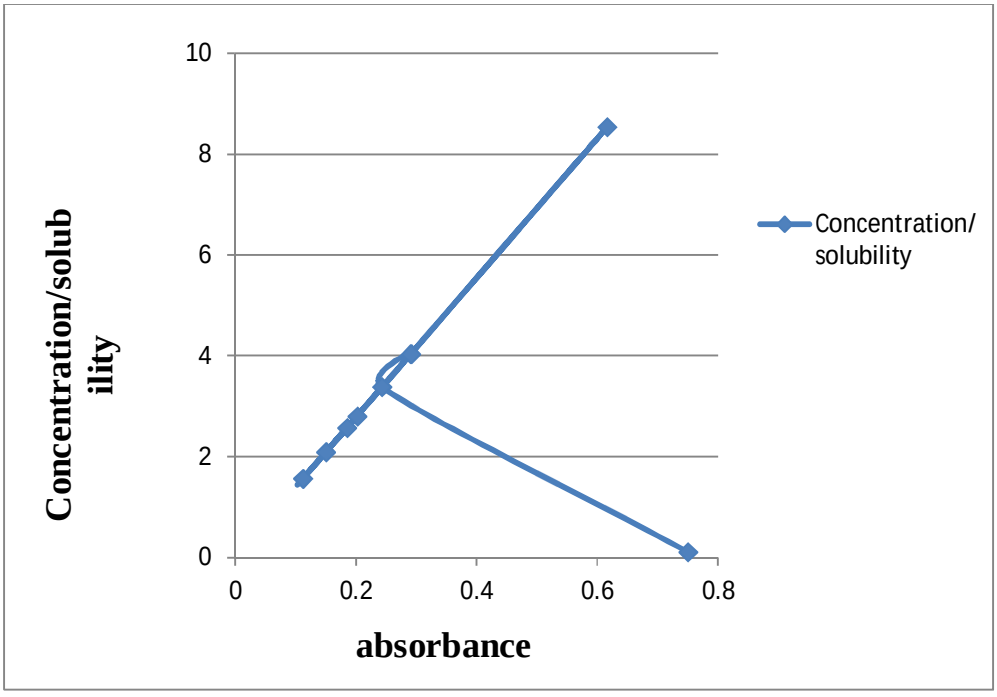

Figure:2

Table: 4 solubility of ibuprofen in various fluids containing PEG 400,PVP K 30 and Tween 80

S:no	contents	Absorbance	Dilution factor	Concentration/solubility
1	Water	0.750	10	0.105
2	Water+2% PEG 400	0.243	1000	3.380
3	Water+2% PVP K30	0.291	1000	4.035
4	Water+2% + PEG 400+ 2% PVP K30	0.112	1000	1.560
5	Water+2% Tween 80	0.616	1000	8.540
6	Water+2% PEG 400+2% Tween 80	0.150	1000	2.09
8	Water+ 2% PVP K 30+ 2% Tween 80	0.202	1000	2.80

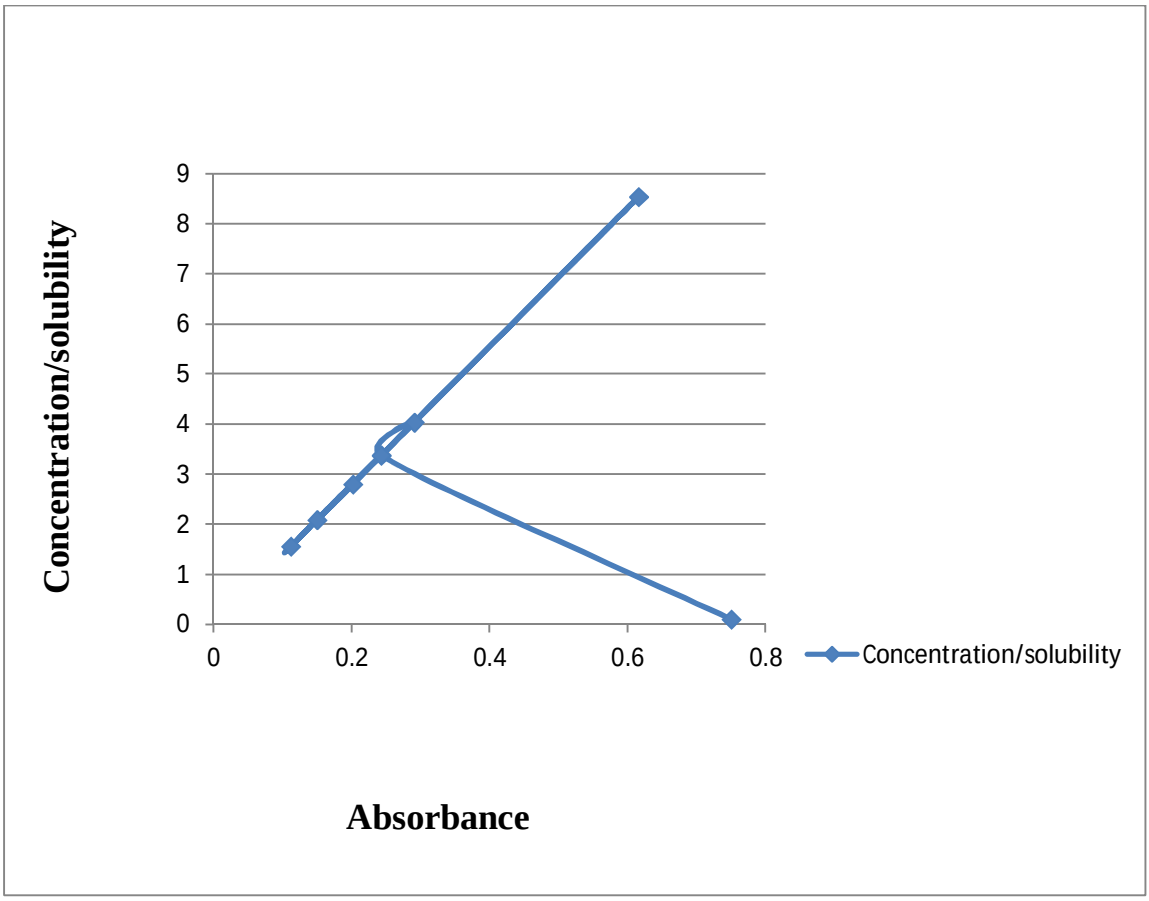

Figure:3

Table 5 : ANNOVA of solubility data:

Source of variance	D.F	S.S	M.S.S	F Ratio	Significance
Total	31	1730558.49	-	-	-
Treatments	7	1731018.10	247288.3	12913.23	P<0.01
F_a	1	172563.44	172563.44	9011.15	P<0.01
F_b	1	49935.40	49935.40	2607.62	P<0.01
F_{ab}	1	1068.37	1068.37	55.79	P<0.01
F_c	1	23983525.97	23983525.97	1252403.44	P<0.01
F_{ac}	1	279957.74	279957.74	14619.20	P<0.01
F_{bc}	1	272783.44	272783.44	14244.57	P<0.01
F_{abc}	1	714879.14	714879.14	37330.50	P<0.01
Error	24	469.61	19.15	--	--

$F_{0.01}(1,24) = 7.823$

$F_{0.01}(7,24) = 2.977$

RESULTS AND DISCUSSION:

The individual main effects and combined (interaction) effects of the 3 factors PVP K 30,PEG 400 and Tween 80 as the aqueous solubility of were evaluated in a 2^3 factorial experiments. For this purpose 2 levels of each factor (0,2%) were selected and the corresponding eight treatments as per 2^3 factorial study as follows:

1.Purified water (all the 3 factors at 1st level)

2.Water contains 2% PEG 400(a),2% PVP K_{30} (b),2% PEG 400 and PVP K_{30} (a,b),2% Tween 80 (c),2% PEG 400 and 2% Tween 80 (a,c),2% PVP K30 and 2% Tween 80 (b,c) ,2% PEG 400, 2% PVP K_{30} and Tween 80 (a,b,c).

The solubility of in the above mentioned fluids was determined (n=4) and the results are given in table 2 .The aqueous solubility of was measured by enhanced by PEG 400,PVP K_{30} and Tween 80 individually as well as in combination. The solubility data of the main subjected to ANOVA to find out the significance of the main and combined effects of PEG 400,PVP K_{30} and Tween 80 on the solubility of ibuprofen .The results of ANOVA are shown in the table 5. The individual and combined effects of PEG 400,PVP K30 and Tween 80 is enhanced in the solubility of ibuprofen were highly significant.Among the three, when tested individually Tween 80 gave higher enhancement in the solubility of ibuprofen (81.36 fold) when compared to PVP K30 (38.43 fold) and PEG 400 (32.20 fold)Among the combinations, PVP K30 and Tween 80 gave higher enhancement (26.68 fold) in the solubility of ibuprofen. The following is the order of increase in solubility of observed with various combination.

bc>abc> ac >ab

PVP K30+Tween 80 > PEG 400+PVP K30+Tween 80 > PEG 400+Tween 80 > PEG 400+PVP K30

CONCULSION:

The individual and combined effects of the three factors namely PEG 400,PVP K 30 and Tween 80 in enhancing the solubility of ibuprofen were evaluated. The individual as well as combined effects of the three factors in enhancing the solubility are highly significant($P < 0.01$).Among the three, when tested individually Tween 80 gave higher enhancement in the solubility of ibuprofen (81.36 fold) when compared to PVP K30 (38.43 fold) and PEG 400 (32.20 fold)**.**Among the combinations, PVP K30 and Tween 80 gave higher enhancement (26.68 fold) in the solubility of ibuprofen. The following is the order of increase in solubility of observed with various combination.

bc>abc> ac >ab

PVP K30+Tween 80 > PEG 400+PVP K30+Tween 80 > PEG 400+Tween 80 > PEG 400+PVP K30

Thus, Tween 80 alone and in combination with PVP K30 and Tween 80- was found to enhance the solubility of ibuprofen.

REFERENCES:

1. Yasir M, Mohd A, Ashwani K, Abhinav A: Biopharmaceutical Classification System: An Account International Journal of PharmTech Research. 2010; 1681-1690.

2. Mahesh Kumar K and Anil B: Biopharmaceutics drug disposition classification system: An Extension of Biopharmaceutics classification system, International research journal of pharmacy ISSN ;2230-8407.

3. Vikash D and Asha K: Role of Biopharmaceutical Classification System In Drug Development Program journal of current pharmaceutical research JCPR 2011; 5: 28-31

4. Anuj K, Sangram K, Kumud P, Prithi P, Singh K, Ajit S and Naveen P:Review On Solubility Enhancement Techniques For Hydrophobic Drugs .PharmacieGlobaleInternational Journal Of Comprehensive Pharmacy 2011; 976-8157.

5. Prudhvi Raj V, Subhashis D, Maleswari T, NiranjanBabu M, BhaskarNaik B.

6. Preparation, Characterization And Evaluation Of Olmesartan Medoxomil-B Cyclodextrin Complexes, Indian Journal Of Research In Pharmacy And Biotechnology Issn: 2321-5674

7. Ketan T. Savjani, Anuradha K. Gajjar, and Jignasa K. Drug Solubility: Importance and Enhancement Techniques. International Scholarly Research Network ISRN Pharmaceutics Volume 2012, Article ID 195727.

8. Kumari R, Chandel P, Kapoor A: Paramount Role of Solid Dispersion in Enhancement of Solubility, Indo Global Journal of Pharmaceutical Sciences 2013; 3: 78-89.

9. Kalia A, Poddar M: Solid Dispersions: An approach towards enhancing dissolution rate. Int J Pharm Pharm. Sci 2011; 3: 9-19.

10. Kalyanwat R, Patel S. Solid Dispersion: A method for enhancing drug dissolution. Int. J. Drug Form. Res 2010; 1: 1-14.

11. Kamalakkannan V, Puratchikody A, Masilamani K, Senthilnathan B. Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review. J Pharm Res 2010; 3: 2314-2321

12. Amit C, Upendra N, Neha G, SharmaVK and KhosaR L:Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review Journal of Advanced Pharmacy Education & Research 2012;2: (1) 32-67.

13. Mohanachandran PS, Sindhumol PG and Kiran TS: Enhancement Of Solubility And Dissolution Rate: An Overview

Mohanachandran P S Et Al. / PharmacieGlobale (Ijcp) 2010; 4 (11)

14. Varun Raj V, Venkateshwarlu L and Srikanth L: Solubility Enhancement Techniques, International Journal Of Pharmaceutical Sciences Review And Research2010; 5: 1

15. http://www.pharmainfo.net/reviews/solubilization-poorly-soluble-drugs-review

16. Solubility. http://www.sciencebyjones.com/Teaching%20Menu.htm

17. Solubility of Solutes and Aqueous Solutions. http://www.chem.lsu.edu/lucid/tutorials/tutorials.html

18. Adam M. Persky and Jeffrey A. Hughes, Solutions and Solubility. http://www.cop.ufl.edu/safezone/prokai/pha5100/pha5110.htm

19. Singha lD and Curatolo W: Drug polymorphism and dosage form design: a practical perspective. Adv Drug Deliv Rev 2004; 56: 335-347.

20. Pinnamaneni S, Das NG and Das SK: Formulation approaches for orally administered poorly soluble drugs. Pharmazie 2002; 57: 291 – 300.

21. Chaumeil JC: Micronisation: a method of improving the bioavailability of poorly solubledrugs, Methods and Findings in Experimental and Clinical Pharmacology 1998; 20: 211-215.

22. Nanosuspension drug delivery Technology and application - Nanotech - Express Pharma Pulse.htm, http://www.expresspharmapulse.com

23. Aulton ME: Pharmaceutics The science of dosage form design, 2nd edition, Churchill Livingstone. London 2002; 113 – 138: 234 – 252.

24. Joseph T:Rubino,Cosolvents and Cosolvency 2002; 1: 658-670. http://www.dekker.com

25. Jeffrey W. Millard FA, Alvarez-Nuezand Yalkowsky SH: Solubilization by cosolvents Establishing useful constants for the log /linear model, International Journal of Pharmaceutics 2002; 245: 153-166.

26. Lynn LB and Michael FC: NanoBio Convergence – Emerging Diagnostic and Therapeutic Applications. bioprocessing & biopartnering 2006; 1-4.

27. Valizadeh H, Nokhodchi A, Qarakhani N, et al: Physicochemical characterization of solid dispersions of indomethacin PEG 6000n Myrj 52 lactose sorbitol dextrin and Eudragit E100. Drug DevInd Pharm 2004; 30: 303-317.

28. Keck CM and Müller RH: Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm 2006; 62: 3-16.

29. Izhar Ahmed and PavaniE: The Liquisolid Technique: Based Drug Delivery System, International Journal of Pharmaceutical Sciences and Drug Research 2012; 4(2): 88-96

30. MudgalSSand Pancholi SS, Formulation of glibenclamide solid dispersions by solvent evaporation technique Journal of Chemical and Pharmaceutical Research 2012; 4(1):353-359.

31. The science and practices of pharmacy by Remington-21 edition volume –I, page no: 229-230.

32. The theory and practice of industrial pharmacy by Lachman, page no:466-467.

33. Indian pharmacopeia volume-I, page no:158.

34. Pharmaceutical excipients-4th edition, editorial by Raymond C Rower, Paul J Sheskey and Paul J Weller. page no:508-513,484-487,479-483.

35. The complete drug reference by martindale-34thedition,page no:45.3-47

36. Pharmaceutical statistics practical and clinical application by sam ford Boltan, Charles Bon, page no:222-239.

37. Basic statistics and pharmaceutical statistical application by 2nd edition by James E De muth. Research journal of pharmaceutical, biological and chemical sciences. Jan-March 2012 vol-3page no: 190.

38. Chowdary KPR ,Surya PRK, A factorial study on the effect of β-Cyclo dextran and poly xamv on the solubility and dissolution rate of piroxicam. IJRPC 2011 :601-605

39. Chowdary KPR., Udaya Chowdary D and Indira M, A factorial study on formulation dept. Of ibuprofen tablet employing ibuprofen starch 1500 and PVP K 30.IJPSR 2012; 3:189-193.

40. KPR Chowdary :A factorial study on enhancing the dissolution rate of nimesulide tablet employing starch citrate-A new modified starch, PEG 400 PVP K 30. IJPR&D 2011; 3:224-230

41. Harisshoaib M, Jaweria T, Hamid AM and Rabiaismail Y:Evalution of drug released kinetics from ibuprofen matrix tablet using HPMC sut 2006; 19(2):119-124.