Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
4(4), 2015, 305-315

ISSN 2321 – 0958

Original Research Article

STUDIES ON MIXED SOLVENCY CONCEPT IN FORMULATION DEVELOPMENT OF ORAL SOLUTION (SYRUP) OF POORLY WATER SOLUBLE DRUGS

Love Kumar Soni[1], Shailendra Singh Solanki[1*], Rajesh Kumar Maheshwari[2]

1. School of Pharmacy, Devi Ahilya University, Takshashila Campus, Indore, Madhya Pradesh, India
2. Department of Pharmacy, Shri G S Institute of Technology and Science, Park Road, Indore- 452003, Madhya Pradesh, India

Abstract: Application of the mixed solvency has been employed in the present research work to develop the oral solution (syrup) formulations of poorly water soluble drugs aceclofenac (as model drug). Due to the low water solubility of aceclofenac in water (0.152 mg/ml), an attempt was made to enhance the solubility of drug by adding cost effective additives (combination of solubilizers as mixed solvent system) which could increase the solubility as well as stabilized the developed oral solution (syrup) formulation. On the basis of solubility studies mixed solvent oral solution formulations of aceclofenac were developed. Formulations were characterized by FTIR and Raman spectroscopy. Various properties of solution such as pH, viscosity, specific gravity and refractive index were also studied. The physical and chemical stability studies were carried out to examine the physical and chemical stability of an optimal oral solution (syrup) formulation of aceclofenac. All the formulations were physically, chemically and microbiologically stable for more than three months.

Keywords: Solubility, Aceclofenac, Aqueous oral solution, Mixed solvency, Nsaids. Polyethylene glycol, Sodium citrate.

1. Introduction: Oral route of drug administration has been used for several years, which is preferred to be most convenient and easy, therefore has been considered most natural, suitable and widely accepted one by patients among all routes of drug administration due to its ease of administration, patient acceptance and cost effective manufacturing process[1]. Oral solutions are clear liquid preparation for oral use containing one or more ingredients dissolved in a suitable vehicle[2]. The Biopharmaceutical Classification System categorized the drug substances with respect to their aqueous solubility and permeability. Class II (poor soluble/permeable) and class IV (poor soluble/poor permeable) are the drugs which require solubility enhancement by which the oral bioavailability of drug compounds can be improved for which the dissolution is usually the rate-limiting step for gastrointestinal

For Correspondence:
sss.solanki@gmail.com
Received on: July 2015
Accepted after revision: October 2015

absorption[3]. To enhance dissolution rate and thus oral absorption of the Class II drugs numerous formulation strategies have been developed. Special techniques are required to solubilize poorly water-soluble drugs. Solubility of drug can be increased by variety of contemporary methods such as hydrotropic solubilization, solid dispersions, inclusion complex formation, altering the pH and using cosolvents but excess amount of these agents may have adverse effects. The term "hydrotropy" have been used to designate the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of a large amount of additives. Concentrated aqueous hydrotropic solutions of urea, nicotinamide, sodium benzoate, sodium salicylate, sodium acetate and sodium citrate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs[4-8].

A drug administered in solution is immediately available for absorption and in most cases is more rapidly and efficiently absorbed than the same amount of drug administered in suspensions. Maheshwari have demonstrated the synergistic solubilizing capability due to mixed hydrotropy approach. They are of the opinion that hydrotropy is another type of co-solvency. Instead of using one solubilizer in large concentration for a desired level of solubility, the concentrated solutions made by employment of several solubilizers in small concentrations may show additive or synergistic enhancement in solubility[9-12].

Maheshwari proposed the concept of mixed solvency. He is of the opinion that all substances whether liquids, gases or solids possess solubilizing power and hence concentrated aqueous solutions containing various dissolved substances can also improve the solubility of poorly water soluble drugs. In supercritical fluid technology liquefied carbon dioxide acts as solvent for many insoluble substances. These indicate that all substances possess some solvent character. This mixed solvency concept may be utilized to prepare the concentrated combined aqueous solutions of various water-soluble additives from the categories of so called, hydrotropes (solid solvent) and co-solvents employing them in small, safe concentrations to solubilize the poorly water-soluble drugs to develop their dosage forms (solutions, syrups, injections, topical solutions etc). Therefore, the authors have proposed a mixed-solvency approach for poorly water-soluble drugs[13-17].

Application of the mixed solvency has been employed in the present research work to develop the oral solution (syrup) formulations of aceclofenac[18] (used as model poorly water soluble drug), it is white crystalline powder, practically insoluble in water, freely soluble in acetone, soluble in ethanol (96%) (Figure 1). Mixed solvency approach may reduce the individual concentration of solubilizers and so reduce their toxicity associated with them. It may reduce the total concentration of solubilizers, necessary to produce modest increase in solubility by employing combination of agents in lower concentrations.

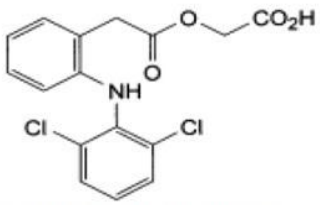

Figure 1: Structure of aceclofenac

2. Materials and Methods

2.1 Materials: Aceclofenac was obtained as gift sample from IPCA Laboratories, Ratlam, India. Propylene glycol were purchased from Loba chemie, Mumbai. Urea, Sodium citrate, Glycerin, PEG 200, PEG 300, PEG 400, PEG 600 and sucrose were obtained from Merck Chemicals Limited, Mumbai, India. All other chemicals and solvents used were of analytical/HPLC grade.

2.2 Estimation of Aceclofenac: In the present investigation, UV spectrophotometric method was used for the estimation of aceclofenac. The calibration curve of aceclofenac was prepared in

distilled water and various concentrations of water soluble solubilizers (solid solubilizers and liquid solubilizers) and mixed solvent at 274 nm using double-beam (UV-1800, Shimadzu, Japan) UV spectrophotometer[9-13].

2.3 Solubility Determination: Solubility of aceclofenac in various solubilizers solutions was determined by equilibrium solubility method. Sufficient excess amount of aceclofenac was added to 10 mL screw-capped glass vials containing 5 ml of aqueous solution of individual solubilizer (40% w/v) (Table 1) mixed solvent system (40% w/v) (Table 2). The vials were shaken mechanically for 12 h on mechanical shaker (Lab Hosp, Mumbai, India) at room temperature. The solutions were allowed to equilibrate for the next 24 hr. The supernatants of each vial were filtered through Whatman filter paper grade 1 and filtrate after appropriate dilution, analyzed for drug content by UV visible spectrophotometer (Shimadzu-1800) at 274 nm. Solubility was determined in triplicate[13-17]. The solubility enhancement ratios were also calculated using following formula

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility in mixed solvent system}}{\text{Solubility in distilled water}}$$

Table 1: Solubility enhancement ratio and ΔG^0tr of aceclofenac in different solubilizers at room temperature.

Solvents	Solubility Ratio	ΔG^0tr $JK^{-1}mol^{-1}$
40% w/v UR	17.57	−7107.10
40% w/v SC	6.19	−4520.31
40% w/v PG	4.77	−3877.14
40% w/v GLY	8.63	−5344.41
40% w/v PEGTH	7.98	−5149.88
40% w/v PEGTHH	10.34	−5792.70
40% w/v PEGFH	9.65	−5.621.29
40% w/v PEGSH	9.09	−5475.09

UR- Urea, SC-Sodium citrate , PG- Propylene glycol, GLY-Glycerin

PEGTH-PEG 200, PEGTHH-PEG 300, PEGFH- PEG 400, PEGSH- PEG 600

Table 2: Mixed solvent for saturated solubility determination of aceclofenac.

Blend Code	Mixed Solvents	Solubility Ratio	ΔG^0tr $JK^{-1}mol^{-1}$
AB10	15%SC + 25% S	113.42	− 11730.85
AB11	15%UR+25% S	140.46	− 12261.02
AB12	5%UR+10%SC+25% S	154.01	− 12489.41
AB13	10%UR+5%SC+25% S	231.84	− 13503.58
AB14	10%SC+10%UR+20% S	168.48	− 12712.12
AB15	5%UR+15%SC+20% S	158.68	− 12563.49
AB16	5%SC+15%UR+20% S	248.28	− 13673.52
AB17	10%UR+5%SC+4%PEFTH+5%PEGTHH+5%PEGFH+7%GLY+4%PG	218.88	− 13360.94
AB18	8%SC+5%UR+5%PEGTH+5%PEGTHH+5%PEGFH+7%GLY+5%PG	102.69	− 11484.58
AB19	8%UR+7%SC+25%S	211.44	− 13275.26

UR- Urea, SC- Sodium citrate, S- Solvent system containing 4 & 5% of each PEG 200, PEG 300, PEG 400, Glycerin and Propylene glycol for 20% and 25% concentration respectively.

2.4 Formulation development of oral solution (syrups)

Based on solubility determination studies, oral solution (syrup) formulations were prepared using the blends of mixed solvent system. The required quantities of all solubilizers were transferred to a volumetric flask (100 ml capacity) containing 50 ml of warm distilled water and the flask was shaken to dissolve the solubilizers, completely. Then, the required amount of aceclofenac drug was added and the flask was shaken to dissolve the drug completely. The required amount of sucrose was added and again the flask was shaken to dissolve it. The flask was kept aside for some time to lower the temperature, then volume was made up to the mark with distilled water and the oral solution was filtered through the filter paper. First few ml of oral solution was discarded and filtered oral solution (syrup) was preserved in airtight container. Then the composition of oral solution formulation containing aceclofenac in the dose of 20 mg/ml was established. The compositions of created oral solutions (syrup) are presented in table 3.

Table 3: Composition of aceclofenac oral solution formulations

Composition % W/V	**Formulation code**		
	AOS 1	AOS2	AOS3
Aceclofenac	2	2	2
Urea	10	10	8
Sodium citrate	5	5	7
PEG 200	5	4	5
PEG 300	5	5	5
PEG 400	5	5	5
Glycerin	5	7	5
Propylene glycol	5	4	5
Sucrose	40	40	40
Distilled water (q.s.)	100	100	100

3. Evaluation of oral solution formulations.

3.1 Drug content analysis: The drug content was determined spectrophotometrically. The syrup formulation (0.5 ml) was diluted sufficient in volumetric flask with distilled water and absorbance of this solution was measured at 274 nm against reagent blank. The drug content was determined using regression equation Y = 0.027X+0.007. Analysis was carried out in triplicate. The results are presented in Table 4.

Table 4: Drug content of different oral solution formulation

Sr. No.	**Formulations**	**% Drug content (mg/10 ml)**
4	AOS1	99.89
5	AOS2	99.80
6	AOS3	99.86

3.2 Determination of physical properties of developed formulation: The physical properties of developed aceclofenac oral solution (syrup) formulations such as pH, viscosity, specific gravity and refractive index were determined using digital pH meter (pHCal, Analab Scintific Instruments Pvt. Ltd. Gujarat, India)., Brookfield viscometer (DV-I PRIME, Brookfield Eng. Lab. Inc. USA), pyknometer and digital refractometer (DG-NXT, Advance Research Instruments Company, New Delhi, India) respectively. The results are presented in Table 5.

Table 5: Properties of the prepared oral solution formulations

Formulations	**pH**	**Viscosity (cps)**	**Specific gravity**	**Refractive index**
AOS4	6.68	38.13	1.202	1.460
AOS5	6.72	38.28	1.203	1.461
AOS6	6.44	37.41	1.201	1.459

3.3 Fourier transform infrared (FTIR) spectral studies

FTIR spectra were obtained by means of a FTIR spectrophotometer (IR Affinity-1, Shimadzu,

Japan) with single reflection quest ATR. A dropping pipette was used to place the liquid sample over ATR crystal surface and measurements were recorded over the range of 400–4000 cm^{-1}. Interaction between the components was indicated by shift in the characteristic peaks corresponding to the drug and solubilizers [5,7]. The FTIR/ATR spectra are presented in figure 2.

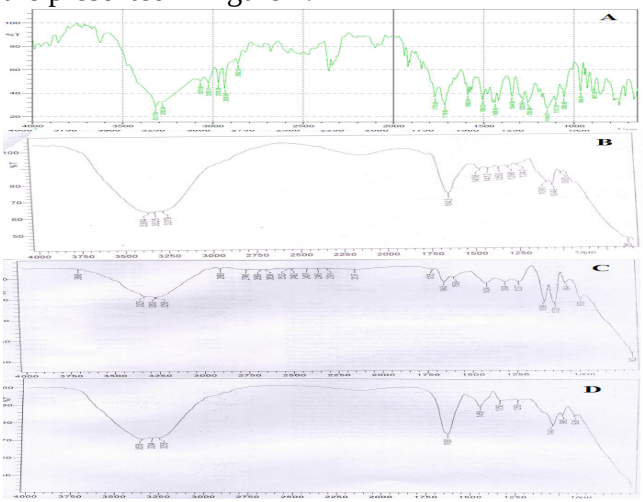

Figure 2: Comparative FTIR spectrum of Pure ACF (A), and formulation AOS1(B) AOS2 (C), AOS3 (D).

3.4 Raman spectroscopic analysis: The Raman spectra were recorded by micro-Raman system (Jobin Yvon Horiba LABRAM-HR visible) using Argon as excitation laser source at wavelength 488 nm. Using confocal optics a lateral resolution of 1 micron and an axial resolution of 2 micron can be achieved. An Olympus BX41 microscope was used with a 50X magnification lens to focus the sample. 600 lines/mm gratings were used for dispersive geometry; the charge-coupled device (CCD) camera was used as the detector with the spectral resolution of 1 cm−1. Laser power of the source was maintained at 2.5-5 mW throughout all measurement with an accumulation time of 5-10 second. The spectra were collected over the wave number range from 3800-400 cm^{-1}. A spectral region between 1000-1700cm^{-1} and 3000-3350 cm^{-1} was selected for raman analysis of Aceclofenac in crystalline state and in solution forms as shown in figure 3 and figure 4.

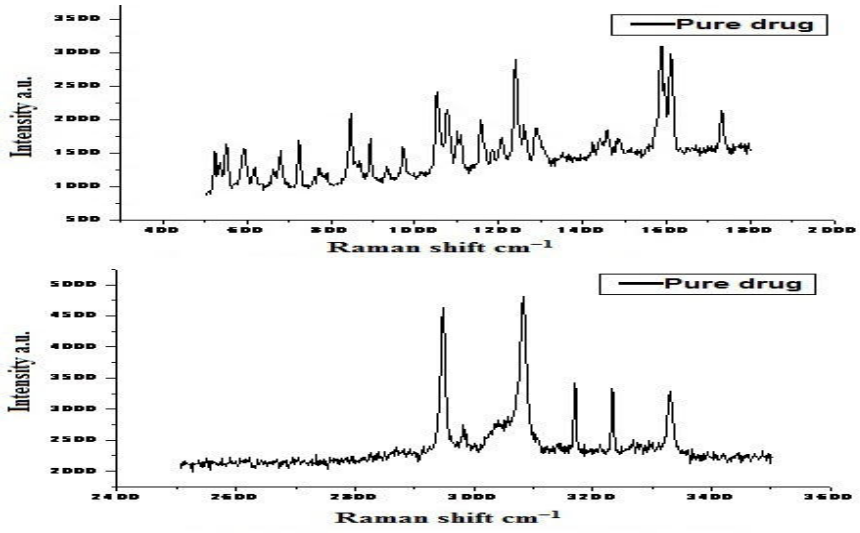

Figure3: Raman spectra of pure drug

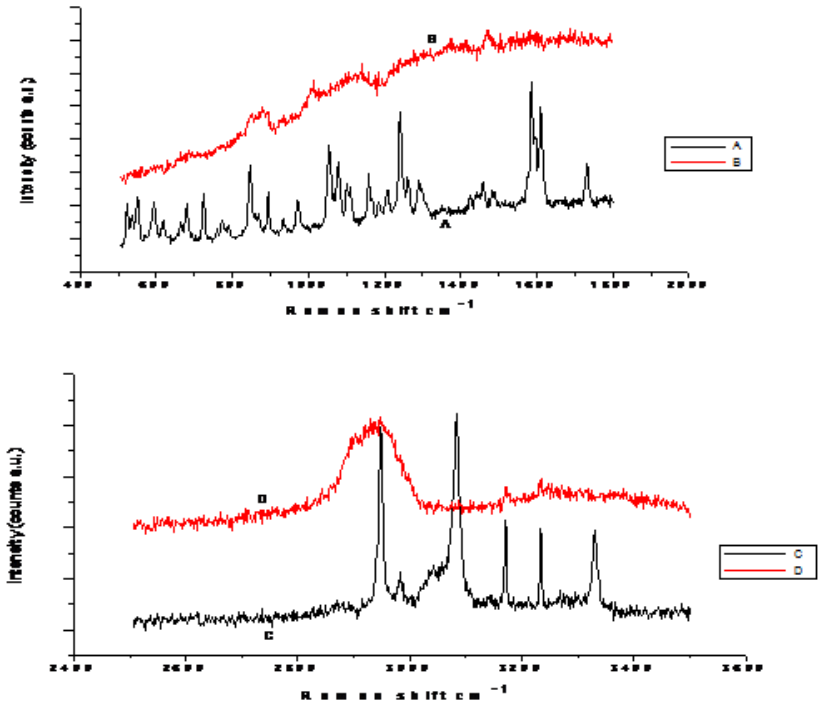

Figure 4: Raman spectra of pure drug compared with oral solution formulation

3.5 Stability studies

3.5.1 Biological stability testing

The test for microbial contamination is the method to establish the presence or absence of viable microorganisms (bacteria and fungi) using the defined culturing method. The microbial contamination test of the non-sterile product is defined by the absence of viable and multiplying microorganisms, as specified in Indian Pharmacopoeia. The test for microbial contamination was performed on non sterile prepared formulation AOS2 and AOS3 according to Indian Pharmacopoeia (IP, 2007)[19]. Observations are presented in table 6.

Table 6: Observation table for microbial contamination test in non sterile product

Formulation code	Culture media used	Observation	Inference
AOS2	Soybean-casein digest medium	No evidence of microbial growth	Comply with the test for microbial contamination
AOS3	Soybean-casein digest medium	No evidence of microbial growth	Comply with the test for microbial contamination

3.5.2 Freeze-thaw cycling studies

In case of products that are susceptible to phase separation, loss of viscosity, precipitation and aggregation, an extra investigation involving thermal cycling is carried out to establish the influence of temperature variation during distribution. Under this, the packaged product is cycled through temperature conditions that simulate the changes likely to be encountered once the drug product is in distribution. The formulated aceclofenac oral solutions (syrups) were subjected to freeze-thaw cycling studies by exposing them alternately at 4°C and 40°C (for 24 h at each temperature) during 14 days. Results are presented in table 7.

Table 7: Freeze-thaw cycling susceptibility studies

Formulations	Condition	Freeze thaw cycling stability			
		Phase separation		Precipitation	
		Initial	After 14 days	Initial	After 14 days
AOS1	4°C±1	Homogeneous solution	Homogeneous solution	No ppt.	No ppt.
	40°C±1	Homogeneous solution	Homogeneous solution	No ppt.	No ppt.
AOS2	4°C±1	Homogeneous solution	Homogeneous solution	No ppt.	No ppt.
	40°C±1	Homogeneous solution	Homogeneous solution	No ppt.	No ppt.
AOS3	4°C±1	Homogeneous solution	Homogeneous solution	No ppt.	No ppt.
	40°C±1	Homogeneous solution	Homogeneous solution	No ppt.	No ppt.

3.5.3 Physical stability testing of formulated syrups

The developed formulations were evaluated under different storage conditions as per the ICH guideline. The syrups were filled in 10 ml colourless glass vials and vials were plugged and sealed. The sealed vials of the oral solution (syrups) were visually inspected for 1, 2 and 3 month against black and white backgrounds to see the changes occurring, if any, in physical appearance of formulations like color, turbidity/precipitation etc. on storage at room temperature, 40°C±2°C/75%RH±5% (BTI-24A stability chamber, Bio Technics, India) and at 55°C in thermostatically controlled ovens (Lab Hosp, Mumbai, India)[20-23]. The results are presented in table 8.

3.5.4 Chemical Stability testing of formulated syrups

The syrups were filled in 10 ml amber color glass vials and vials were plugged and sealed. The oral solution (syrup) formulation were subjected to exhaustive chemical stability at room temperature, 40°C±2°C/75%RH±5% (BTI-24A stability chamber, Bio Technics, India) and at 55°C in thermostatically controlled ovens for a period of 3 months. The formulations were analyzed spectrophotometrically initially and at particular intervals to calculate the drug content[20-23]. The percent residual drug at different time intervals as well as at different temperatures was calculated considering the initial drug content for each formulation to be 100%. The results are presented in table 8.

.

Table 8: Physical and chemical stability data of formulation AOS1, AOS2 and AOS3

Formulation Code	Temp.	0 Day			1 Month			2 Month			3 Month		
		Color	ppt	% Residual drug	Color	ppt	% Residual drug	Color	ppt	% Residual drug	Color	ppt	% Residual drug
AOS1	RT	Colorless	No ppt	100	Colorless	No ppt	98.88±0.569	Colorless	No ppt	97.03±0.953	Colorless	No ppt	96.59±0.916
	40± 2°C	Colorless	No ppt	100	Colorless	No ppt	96.52±0.469	Colorless	No ppt	92.65±0.759	Pale yellow	No ppt	87.21±1.129
	55± 1°C	Colorless	No ppt	100	Pale yellow	No ppt	88.96±1.635	Deep pale yellow	No ppt	76.64±1.584	Deep reddish color	No ppt	#
AOS2	RT	Colorless	No ppt	100	Colorless	No ppt	98.62±0.473	Colorless	No ppt	97.48±0.994	Colorless	No ppt	96.83±0.663
	40± 2°C	Colorless	No ppt	100	Colorless	No ppt	96.10±0.814	Colorless	No ppt	91.52±1.049	Pale yellow	No ppt	87.68±1.182
	55± 1°C	Colorless	No ppt	100	Pale yellow	No ppt	84.35±1.295	Deep pale yellow	No ppt	69.52±1.683	Deep reddish color	No ppt	#
AOS3	RT	Colorless	No ppt	100	Colorless	No ppt	98.13±0.439	Colorless	No ppt	97.90±0.332	Colorless	No ppt	95.81±0.663
	40± 2°C	Colorless	No ppt	100	Colorless	No ppt	97.13±0.639	Colorless	No ppt	93.52±1.048	Pale yellow	No ppt	90.26±1.176
	55± 1°C	Colorless	No ppt	100	Pale yellow	No ppt	86.54±1.318	Deep pale yellow	No ppt	69.72±1.571	Deep reddish color	No ppt	#

Deep reddish colors were developed in all oral solution formulations during 3 months of storage and hence were discarded and further studies at 55°C were terminated.

4. Results and Discussion

The drug contents for prepared formulations were within the pharmacopoeial limit.

The various solution properties of prepared formulations were studied and pH of the formulations was found to be near about neutral and was in range of 6.44 to 6.72. The viscosity of all the solutions were deviate with the slight changes in the concentration and was found to be between 37.41 to 38.28 cps., while the specific gravity of solutions were again slight deviated because of change in concentration of solubilizers in solutions and was found in ranged from 1.201 to 1.203. The experimental values of refractive index showed that developed oral solution formulations were homogeneous, single phase, colorless clear solution with refractive index between 1.459 - 1.461.

The IR spectral analysis of aceclofenac alone showed that, the principle peaks were observed at wave numbers of 3317.56 cm^{-1} (N-H stretching vibration for amine), 3282.84 cm^{-1} (O-H stretching), 3026 and 3070 cm^{-1} (aromatic C-H stretching), 1770.64 (C=O stretching of -COOH), 1716.65 cm^{-1} (C=O stretching of COO^{-}) and band observe at 1589 and 1438 cm^{-1} due to N-H and O-H bending respectively, confirming the purity of the drug as per the established standards (figure 2). In the IR spectra of the aceclofenac in oral solution formulation, the major peaks of aceclofenac in selected formulation were sifted to higher wave number for OH stretching and lower wave number for CO group of drug. All the oral solution formulation retain the similar peaks to some extent, OH group shows a broad band with stretching vibration in region 3400 cm^{-1} to 3200 cm^{-1} and slight shifting of peak was strong indication of intermolecular hydrogen bonding and Van der Waals interaction. In solution formulation peaks are slight shifted towards higher wavenumber 3325 cm^{-1} (B and C), 3356 cm^{-1} (D) (O-H stretching) and at lower wavenumber 1648 cm^{-1} (B), 1705 cm^{-1}, and 1643 cm^{-1} (C), 1636 cm^{-1} (D) (carboxylic C=O group streching) which might be interpreted as consequences of hydrogen bonding and electrostatic interaction between pure drug and mixed solvent system.

When observing the Raman spectra of pure aceclofenac and oral solution (syrup) formulation, clean differences can be seen at two main spectral region, the one region of interest was 1000-1800 cm^{-1} where peak at 1729 cm^{-1} was due to monomeric carboxylic acid and the peak at 1610 cm^{-1} and 1586 cm^{-1} are given by phenyl ring stretching (C-C and C-N) vibrations. The second region of interest was 2500-3500 cm^{-1} where the peak was observed at 3330 cm^{-1} assigned to N-H stretching vibration, the band observed at 3234 cm^{-1} was due to O-H stretching vibrational mode. The band of C-H stretching mode falls in the region of 2946–3170 cm^{-1} for aromatic C-H stretching vibration. In both these regions the intensity of characteristic peaks were reduced, broadened and had narrower shaped with variable width and frequency. The peaks were also slight shifted towards their lower wave number in liquid formulation spectra. This expected shifting in peaks may be exhibited by drug-solubilizers hydrogen bonding network formation or interaction. The vibrational mode will be affected more in liquid formulation than that of the rigid structure of pure crystalline drug. The C-H stretching mode observed weak in FTIR due to low polarity but these C-H stretching modes are stronger in Raman spectrum. Thus the spectral difference in these two regions can be explained by observing differences in the Raman band because of intermolecular interaction of drug with solubilizers in solution and difference in crystal symmetry of pure aceclofenac.

Test for microbial contamination in non sterile product was performed to check for presence of any viable and multiplying microorganism in developed oral solution formulation. No evidence of microbial contamination was observed in the test samples. In positive control test, colonies of microorganisms were observed

and this showed that media support the growth of microorganisms. The prepared formulations were free from microorganism which indicated that higher osmotic pressure in solution may be responsible for self preservation of developed formulation. All tested formulations comply with pharmacopeial test for microbial contamination.

All syrups were subjected to freeze-thaw studies at $4^{o}C\pm1$ and $40^{o}C\pm1$ (for 24 h at each temperature) during 14 days. No phase separation or precipitations were observed in oral solution (syrup) formulations.

All formulations were subjected to physical and chemical stability studies. The stability protocol consisted of storage of formulations in sealed vials at different temperature and humidity. The observations were made in respect of change in color and occurrence of any precipitation. From the results it is evident that syrups remained colorless at room temperature after storage for 3 months. When stored at 40°C±2°C/75%RH±5%, all the formulations showed change in color from colorless to pale yellow during 3 month. All the formulations turned to pale yellow color during one month at 55°C and subsequently turned to deep pale yellow to deep reddish color during 2 month and 3 month respectively.

The results of chemical stability studies of all formulation showed that the residual drug content were more than 95.00% at room temperature at the end of 3 month. The residual drug contents were found to be 96.10% to 97.13% in all formulations during one month at 40°C±2°C/75%RH±5%. The residual drug contents were found to be 87.21% to 90.26% during 3 months at 40°C±2°C/75%RH±5% in all formulations. At 55 °C the residual drug content was less than 90.00% during 1 month in all formulations and were less than 80.00% during the 2 months of storage. Deep reddish colors were developed at $55^{o}C$ in all oral solution formulations during 3 months of storage and hence were discarded and further studies at $55^{o}C$ were terminated. All the formulations remained clear and no sign of crystal growth, precipitation or turbidity was observed in all formulations during three month of studies.

5. Conclusion

In the present investigation the oral solution of aceclofenac were also developed using the mixed solvent system which showed appreciable physicochemical parameters. The stability studies of developed formulations reveled that oral solutions (syrups) were stable at neutral pH during 3 months when stored at room temperature. The results showed that hydrophobic drugs can be dissolved easily in the mixed solvent system. The developed formulation were free from the microbial contamination and did not show any crystal growth. The mixed solvent system improved shelf-life and chemical stability of oral solution formulations. Mixed solvency method is new, simple, eco friendly, economic, free from pollution. Other poorly water soluble drug may be tried to get solubilized by mixed solvency approach to develop pharmaceutical dosage form, precluding the use of organic solvents. Mixed solvency approach will lead to tremendous progress in bringing new and innovative products to the market.

References

1. Jafar M, Aejaz A, Studies on readymix suspension of ampicillin trihydrate: development, characterization and invitro evaluation. Int. J. Pharmacy Pharm. Sci., 2010, 2(2): 109-112.
2. The international Pharmacopoeia. 2011. 4th edition, 2nd suppl.; WHO press, Geneva, Switzerland.
3. Amidon GL, Lennernas H, Shah VP, Crison JR, A theoretical basis for a biopharmaceutic drug classification: the correlation of in Vitro drug product dissolution and in Vivo bioavailability. Pharm. Res., 1995, 12: 413-420.
4. Maheshwari RK, Analysis of frusemide by application of hydrotropic solubilization

phenomenon. The Indian Pharmacist., 2005, 4: 555-558.
5. Maheshwari RK, New application of hydrotropic solublization in the spectrophotometric estimation of ketoprofen in tablet dosage form. Pharma Review., 2005, 3: 123-125.
6. Maheshwari RK, A novel application of hydrotropic solublization in the analysis of bulk samples of ketoprofen and salicylic acid. Asian J. Chem., 2006, 18: 393-396.
7. Maheshwari RK, Novel application of hydrotropic solubilization in the spectrophotometric analysis of tinidazole in dosage form. Asian J. Chem., 2006, 18: 640-644.
8. Maheshwari RK, Application of hydrotropic solubilization in the analysis of aceclofenac. Asian J. Chem., 2006, 18: 1572-1574.
9. Maheshwari RK, Solid dispersion and syrup formulation of poorly water soluble drug by hydrotropy. The Indian Pharmacist., 2006, 5: 87-90.
10. Maheshwari RK, Jagwani Y. Mixed hydrotropy: Novel science of solubility enhancement. Indian J. Pharm. Sci., 2011, 73: 179-183.
11. Maheshwari RK, Juneja C, Juneja N, Appication of mixed hydrotropic solubilization concept in Spectrophotometric analysis of frudemide in tablet dosage form. T. Ph. Res., 2010, 3: 243-248.
12. Maheshwari RK, Novel application of hydrotropic solubilization in the spectrophotometric analysis of tinidazole in dosage form. Asian J. Chem., 2006, 18: 640-644.
13. Maheshwari RK, Solubilization of ibuprofen by mixed solvency approach. The Indian Pharmacist., 2009, 8: 81-84.
14. Maheshwari RK, A novel concept for solubilization of poorly water soluble drugs. Journal of Technology and Engineering Sciences., 2009, 1: .39-44.
15. Maheshwari RK, Mixed-solvency approach – a boon for solubilization of poorly water soluble drugs. Asian J. Pharmaceutics., 2010, 4: 60-63.
16. Solanki, SS, Soni, LK, Maheshwari RK, Study on mixed solvency concept in formulation development of aqueous injection of poorly water soluble drug. J. Pharmaceutics., 2013, 1-8.
17. Soni, LK, Solanki, SS, Maheshwari RK, Solubilization of poorly water soluble drug using mixed solvency approach for aqueous injection. Br. J. Pharm. Res., 2014, 4: 549-568.
18. British Pharmacopeia. 2009 Volume I. London: The Stationary Office, department of health : British Pharmacopeia Commission, 2009, p. 78-82.
19. Indian Pharmacopoeia 2007 Volume I. Ghaziabad: The Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare; 2007. Microbial contamination. p. 35-44.
20. Welk B, Kurczewska U, Orszulak-Michalak D, Attempts at formulation of syrup with theophylline. Acta Pol. Pharm-Drug Res., 2001, 58: 195-198.
21. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. Annex 2. WHO Technical Report Series, No. 953, 2009.
22. Martin A, Editor. Physical pharmacy and pharmaceutical sciences. vol. 4. Lippincott Williams and Wilikins, New York: USA: 2006.
23. ICH Hormonised Tripartite Guideline: Stability testing of new drug substances and products Q1A (R2). 2003.