WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 1, 1040-1047. Research Article ISSN 2277–7105

SOLUBILITY ENHANCEMENT OF INDOMETHACIN BY FORMING SOLIDDISPERSION USING MIXED HYDROTROPY

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Article Received on
11 Nov. 2021,

Revised on 01 Dec. 2021,
Accepted on 23 Dec. 2021

DOI: 10.20959/wjpr20221-22567

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ABSTRACT

Most of the newly invented chemical drug moieties are poorly water soluble. According to BCS classification, class II and IV drugs are considered as poorly water soluble. So, enhancement of oral absorption and bioavailability of solid dosage forms remains a challenge to formulation scientists due to their solubility criteria. Therefore many techniques are being explored to enhance the solubility of poor soluble drugs. Solid dispersion is one of the most important method for enhance the solubility (dissolution rate) and hence oral bioavailability of poorly soluble drugs. In solid dispersion the particle size of drug is reduced or a crystalline pure drug is converted into amorphous form and hence the solubility is increased. Polymer incorporating in solid dispersion technology is usually hydrophilicin nature and also showing compatibility with the drug to enhance the drug solubility. This review mainly discus about solid dispersion, preparation methods, and finally characterization.

KEYWORDS: Bioavailability, indomethacin, mixed hydrotropy, solid dispersions.

INTRODUCTION

Among the newly developed drug molecules, most of them are lipophilic in nature and poor solubility is one of the most difficult problem of these drugs. Hydrotropy is one of the advanced and most successful method, in which aqueous solubility of poorly water soluble drugs is increased by co- dissolving with other highly water soluble inert substances. Such agents used to increase the solubility of poorly water soluble drug in aqueous medium are known as hydrotropic agent or hydrotropes like Sodium Benzoate, Sodium Citrate, Sodium

Acetate and Urea. Moreover blends of hydrotropes could be used to enhance the solubility of poorly water soluble drugs owing to synergistic or additive effect of solubilizers in combination known as mixed hydrotropy. Mixed hydrotropy tends to decrease the concentration of individual solubilizers and toxicity. Further, all the solubilizers used in the study are GRAS (Generally regarded as safe) listed. Indomethacin is chemically 2--[1-(4-chlorobenzoyl)-5- methoxy-2-methylindol-3-yl] acetic acid. It is pale-yellow to yellow-tan, crystalline powder. It is soluble in ethanol, ether, acetone, caster oil; practically insoluble in water. Indomethacin is a non- steroidal anti-inflammatory agent (NSAIDS) that inhibits the enzyme cyclooxygenase necessary for the formation of prostaglandins and other autacoids. It also inhibits the motility of polymorph nuclear leukocytes.

The aim of the present investigation is to increase the solubility of indomethacin by mixed hydrotropyapproach.

MATERIALS AND METHODS

Materials

Indomethacin was kindly donated by Cipla Limited, Indore. Sodium citrate, sodium acetate, sodium benzoate, urea was kindly donated by Ipca Laboratories Pvt. Ltd., indore. All the chemical and reagents used were of analytical grade.

METHODS

Preformulation Study Determination of Melting Point

The melting point was determined by the capillary method. In that method presealed capillary was filled with small amount of drug and placed in melting point apparatus. The temperature at which drug melts was recorded. This was performed thrice and average value was noted.

RESULT AND DISCUSSION

The melting point average value of indomethacin is 157.3.

Determination of λ_{max} By UV Spectrophotometer

50mg standard indomethacin was weighed accurately and transferred to a 100ml volumetric flask and dissolved in 30 ml of 30% w/v sodium benzoate solution. The flask was shaken and volume was made up to the mark with DM water to give a solution of 1000 µg/ml. The solution thus produced was sufficiently diluted with de-mineralized water to obtain 50µg/ml solution. A reagent blank was prepared by diluting 30 ml of 30% benzoate of soda up to 100

ml with de-mineralized water. From this solution 5 ml sample was pipetted out and diluted up to 100 ml. It was scanned on a double-beam UV-visible spectrophotometer (Shimadzu® 1700) between wavelength 200nm-400nm and the U.V spectrum was recorded (Fig. No:-1).

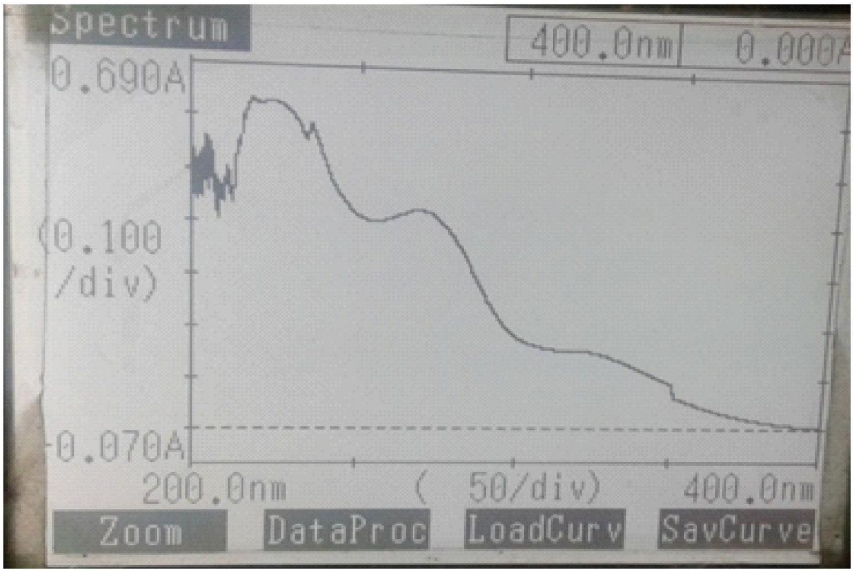

Fig 1: UV Spectrum of indomethacin.

Preparation of calibrationcurve of Indomethacin

50mg of indomethacin was taken in 100ml volumetric flask. It was dissolved in an 30 ml of 30% wlvsodium benzoate solution and the volume was made upto 100ml with DM water to obtain a stock solution of 1000 µg/ml from the above stock solution appropriate dilutions were made in the concentration range 5, 10, 15, 20, and 25 µg/ml and absorbance was taken at **λmax** 320nm. The absorbance were noted taken against reagent blank.

Table 1: Data for calibration curve of indomethacin.

S.no	Concentration(mcg/ml)	Absorbance(mean)±S.D
1	0	0
2	5	0.113
3	10	0.220
4	15	0.306
5	20	0.400
6	25	0.501

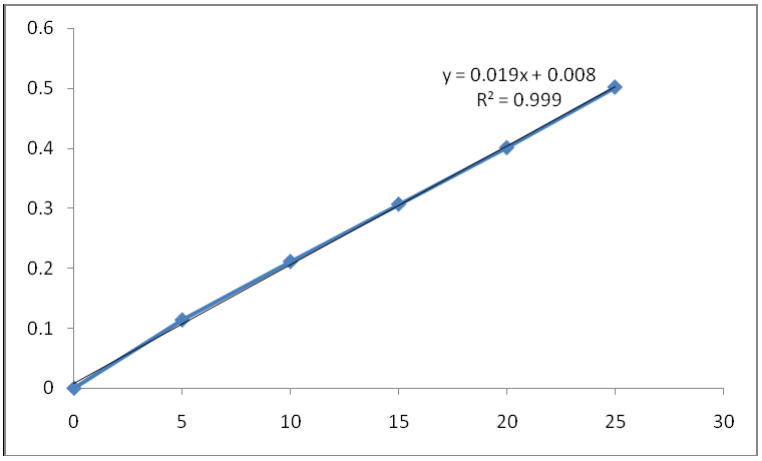

Fig 2: Calibration curve of IndomethacinSolubility determined in hydrotropic agent.

Initially+ solubility of indomethacin was determined individually in solution of 4 hydrotropic agents namely urea (U), sodium benzoate (SA), sodium benzoate (SB), sodium citrate (SC) at concentration of 10%, 20%, 30%, 40% solution using purified water as solvent (Tab. 2). For determining solubility, accurately measured 2 ml of particular blend of hydrotropic agent was taken in a 10 ml volumetric flask and excess amount of drug was added and mechanically shaken until saturated solution was formed the volumetric flask was shaken on mechanical shaker for 12hr that equilibrium solubility can be achieved and solution was allowed to equilibrate for 24 hr. then solution was centrifuged at 2000 rpm for 5 min in ultra-centrifuge and then solution was filtered through whatman filter. Aliquot was suitably diluted with purified water and analysed using UV spectrophotometer at 320nm. From the result of above studies it was concluded that solubility of indomethacin was increasing with increasing concentration of hydrotropic agents, for example solubility in 40% urea solution was foundto be much higher than solubility in 10%, 20% or 30% urea solution. However, highest solubility was obtained in 40% sodium benzoate solution. Then, different combination of above-mentioned 4 hydrotropic agents in different ratios were tried to determine enhancement in solubility, so that t total concentration of hydrotropic agents was always 40% w/v (Tab. 3 & Tab. 4). The blend Urea+Sodium Benzoate+Sodium Citrate in ratio of 15:20:5 gave the highest solubility enhancement, and therefore, this optimized combination of hydrotrop was selected for the preparation of solid dispersions.

Table 2: Solubility of indomethacin in different hydrotropic agents.

Hydrotropic Agents	Concentration (w/v)				Solubility enhancement ratio
	10%	20%	30%	40%	
Urea	0.062	0.091	0.129	0.189	21.000
Sodium Acetate	0.012	0.075	0.140	0.228	25.333
Sodium Benzoate	0.279	0.612	1.170	2.152	239.111
Sodium Citrate	0.014	0.032	0.059	0.127	14.111

Table 3: Solubility of indomethacin in mixture different of hydrotropic agents.

Combination blend	Total Con. (%w/v)	Individual conc. (%w/v)	Solubility (%w/v)	Solubility enhancement ratio
U +SA	40.00	20.00	0.649	72.111
U +SB	40.00	20.00	2.904	322.666
U + SC	40.00	20.00	0.942	104.666
SA + SB	40.00	20.00	2.146	238.444
SA + SC	40.00	20.00	0.064	7.111
SB + SC	40.00	20.00	3.003	333.666
U+SA+SB	40.00	13.33	1.920	213.333
U+SA+SC	40.00	13.33	0.240	26.666
A+SB+SC	40.00	13.33	0.929	103.222
U+SB+SC	40.00	13.33	3.953	439.555

U= urea, SA= sodium acetate, SB = sodium benzoate, SC = sodium citrate

Table 4: Solubility of indomethacin in mixture different of hydrotropic agents.

Combination Blend	Total Con. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancemen tratio
U+SB+SC	40.00	10:20:10	3.991	443.444
U+SB+SC	40.00	10:10:20	1.920	213.333
U+SB+SC	40.00	15:20:5	5.385	598.333
U+SB+SC	40.00	5:20:15	3.301	366.777
U+SA+SB+SC	40.00	10:10:10:10	1.175	130.555
U+SA+SB+SC	40.00	5:5:10:20	1.901	211.222
U+SA+SB+SC	40.00	5:20:10:5	1.112	123.555
U+SA+SB+SC	40.00	20:5:10:5	3.110	345.555
U+SA+SB+SC	40.00	10:5:20:5	4.601	511.222
U+SA+SB+SC	40.00	15:5:15:5	4.330	481.111

U= urea, SA= sodium acetate, SB = sodium benzoate, SC = sodium citrate

Preparation of solid dispersion

For preparation of hydrotropic solid dispersion, accurately weighed urea, sodium benzoate, sodium citrate were taken in a beaker and were mixed properly. Then, minimum possible quantity of warmpurified water sufficient to dissolve the above mixture was added.

Dissolution of the hydrotropic mixture was facilitated by agitation of a Teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of hydrotropic mixture, indomethacin was dissolved in the above solution and temperature was maintained in the range of 55-60º so as to facilitate the evaporation of water. As evaporation proceeded, speed of rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet). The wet solid dispersion thus obtained were spread on several watch glasses and the watch glasses were kept in hot air dry oven maintained at 50±2º so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve # 60 and were finally stored in an airtight glass bottle.

Dissolution rate studies

Solid dispersion or physical mixture equivalent to 20 mg of indomethacin were tested in dissolution rate studies using U.S.P. XXIV (type II) dissolution test apparatus (Model TDT6P, Electro lab Mumbai, India) with paddle to rotate at 50 r.p.m. 900 ml of water was taken as dissolution media withtemp of 37 $\pm$ 0.5 °C. At some definite time interval 20 ml of sample were withdrawn and were analysed for drug content. Withdrawn samples also replaced with fresh dissolution media.

Calculations for the amount of drug were done using respective regression equations and the results ofthe dissolution studies are recorded in table 6.

Table 5: Dissolution of solid dispersion.

Time (min)	% Drug dissolved (solid dispersion)
1	99.82
5	99.15
10	98.20
20	98.03
30	97.65

Micrometric Properties

Micrometric properties of the solid dispersion studied were bulk density, tapped density, compressibility index, are reported in Table 7.

Table 6: Micromeritic properties of solid dispersions.

Parameter	Result
Bulk Density (gm/cm^3)	0.804
Tapped Density (gm/cm^3)	0.813
Compressibility Index	15.901
Hauser Ratio	1.313
Angle of repose	33^o

RESULT AND DISCUSSION

Now days so many techniques and methods are there to improve the solubility and oral bioavailabilityof solid dosage forms of having poorly water soluble drugs. mixed hydrotropy Solid dispersion is one of the approaches to achieve the goal of enhancing the solubility of poorly water soluble drugs.

Manufacturing of solid dispersions requires a suitable combination of drug and carriers. Whatever thistechnology is also highly potential to formulate controlled release dosage forms as the carriers may enhance or delay drug release.

It is evident from dissolution rate studies that solid dispersions were dissolved completely within 1 min, and when observed visually, they were found to be dissolved only within 10-20 s. While, on the other hand, conventional tablet does not get dissolved completely even after 30 min.

The closeness of values of bulk density and tapped density indicates the free flowing property of solid dispersions. The values of compressibility index, Hausner ratio and angle of repose indicate that the flow character of solid dispersion is fair and no aid is needed to increase the flow properties.

REFERENCES

1. Maheshwari RK. A novel application of hydrotropic solubilization in the analysis of bulk samplesof ketoprofen and salicylic acid. Asian J Chem, 2006; 18: 393-6.
2. Maheshwari RK. New application of hydrotropic solubilization in the spectrophotometric estimation of ketoprofen in tablet dosage form. Pharm Rev, 2005; 18: 123-5.
3. Maheshwari RK. Application of hydrotropic solubilization in the analysis of aceclofenac. Asian JChem, 2006; 18: 1572-4.
4. Maheshwari RK. Analysis of frusemide by application of hydrotropic solubilization phenomenon.Indian Pharmacist, 2005; 34: 558.

5. Maheshwari RK. Spectrophotometric determination of cefixime in tablets by hydrotropic solubilization phenomenon. Indian Pharmacist, 2005; 36: 63-8.
6. Maheshwari RK. Novel application of hydrotropic solubilization in the spectrophotometric analysisof tinidazole in dosage form. Asian J Chem, 2006; 18: 640-4.
7. Maheshwari RK. Spectrophotometric analysis of amoxycillin in tablets using hydrotropic solubilization technique. Asian J Chem, 2006; 18: 3194-6.