Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 1, 2013

Research Article

IMPROVEMENT IN PHYSICOCHEMICAL PROPERTIES OF ACECLOFENAC BY USING CHITOSAN AND WATER SOLUBLE CHITOSAN

YOGESHKUMAR N. GAVHANE[1], ADHIKRAO V. YADAV[2]

[1]Department of Pharmaceutics, Government College of Pharmacy, Karad, Maharashtra, India. Pin 415124, [2]Gaurishankar Educational and Charitable Trust's Gaurishankar Institute of Pharmaceutical Education and Research Limb, Satara, (MS) India. Pin 415015
Email: gavhaneyogesh@rediffmail.com

Received: 03 Jan 2013, Revised and Accepted: 11 Feb 2013

ABSTRACT

Objective: The objective of the present study was to investigate and compare the feasibility of Chitosan and water soluble Chitosan derivative to enhance Aceclofenac dissolution.

Methods: Aceclofenac was size reduced and polymer was precipitated on it. Drug-polymer compatibility was accessed using Infrared spectroscopy and Differential Scanning Calorimetry (DSC). Effect of polymer aqueous solubility and polymer: drug ratios on solubility enhancement of drug were studied. Aceclofenac microparticles were subjected to micromeritic properties including angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, and particle size determination. Microparticles were subjected to in vitro drug release and solubility analysis. Results were assayed statistically using one way analysis of variance (ANOVA).

Results: The prepared microparticles were white, free-flowing and crystalline in nature. Microparticles of both the polymers had shown very good flow property and compression behavior at all ratios. The particle size of drug was drastically reduced during formulation. The dissolution studies demonstrated a marked increase in the dissolution rate in comparison with pure drug. Result was more significant for Chitosan chlorhydrate than the Chitosan. DSC showed reduction in melting enthalpy of formulation. DSC results were statistically higher for Chitosan chlorhydrate than Chitosan.

Conclusion: The considerable improvement in the dissolution rate of Aceclofenac from prepared microparticles was due to decreased drug crystallinity, altered surface morphology and micronization. Significant higher effect of Chitosan chlorhydrate than the Chitosan might be attributed to its higher wetting property.

Keywords: Aceclofenac, Chitosan, Chitosan chlorhydrate, Solubility, dissolution

INTRODUCTION

In order to achieve better therapeutic effect the drug should be absorbed from gastro- intestinal tract (GIT) in systemic circulation [1]. And the absorption of drug depends upon solubility and dissolution of drug [1]. Mainly BCS class II drugs have disadvantage of variable solubility because they are characterized by low solubility and high permeability. These drugs show erratic absorption from GIT as solubility and dissolution is less. Thus bioavailability as well as therapeutic response will depend upon solubility and dissolution. [2, 3]. To overcome the said disadvantages large numbers of methods have been developed. The available methods are formation of salts [4], use of polymorphs [5], solid dispersions [6], Use of complexing agents [7], Micronization [8], Nanosuspension [9], Cocrystalisation [10], and use of Chitosan and Chitosan derivatives [11].

Aceclofenac (Fig 1) chemically is 2-[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxyacetic acid [12].

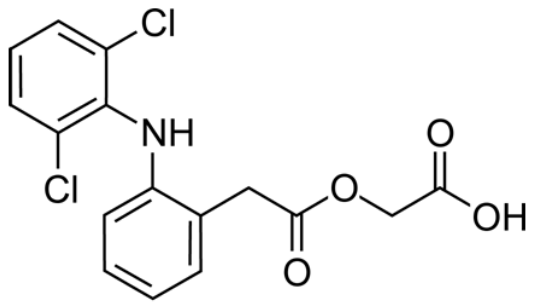

Fig. 1: Chemical structure of Aceclofenac

Aceclofenac is a novel NSAID and it is mainly indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [13]. It acts by blocking the action of cyclo-oxygenase which is involved in the production of prostaglandins responsible for pain, swelling and inflammation [12]. However it is reported that Aceclofenac is practically insoluble in water thus affecting its rate of absorption and ultimately its bioavailability [12]. Moreover when administered orally it causes gastric disturbances like nausea and diarrhea. Reports of gastric ulceration and gastrointestinal bleeding have also noticed in some cases [14, 15].

Chitosan and its derivatives were used in preparation of microparticles. Chitosan is obtained from deacetylization of naturally occurring polysaccharide chitin and it is safe, biocompatible and biodegradable material. Large number of applications of Chitosan has been discovered. One of the best applications of use of Chitosan is dissolution enhancement. Moreover different derivatives of Chitosan has been synthesized which differ in molecular weight and viscosity due to varying degree of deacetylization.[16]

The present work was oriented to improve physicochemical properties of Aceclofenac using Chitosan and its derivatives mainly solubility and dissolution. Microparticles of Aceclofenac with Chitosan and Chitosan chlorhydrate were prepared in different ratios by solvent precipitation method. The prepared formulation were subjected to different evaluation tests like solubility analysis, in vitro dissolution study, evaluation of micromeritic properties, particle size determination and DSC.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Cipla Mumbai. Chitosan and Chitosan chlorhydrate was gift sample from Mahatani Chitosan, Ahmedabad. All solvents were pure analytical grade purchased from Loba Chemie, Mumbai, India. Double distilled water was used throughout the experiment.

Methods

Preparation of microparticles of Aceclofenac with Chitosan and Chitosan chlorhydrate.

A fixed amount of the drug was dispersed separately in Chitosan and Chitosan chlorhydrate solution of different concentrations (0.1, 0.2, 0.5, 1%) prepared in 1% acetic acid solution; which was then precipitated by Trisodium citrate solution, and precipitate was filtered, dried and sieved. A control formulation without any type of Chitosan was also prepared. Different polymer: drug ratios (1:0.1, 1:0.2, 1:0.5, 1:1) were prepared and evaluated.

Evaluation of Formulation

Drug Content

The formulations (10 mg) were triturated and dissolved in 10 mL methanol and volume was made up to 100 mL with water by sonicating for 15 minutes. The solution was filtered through Whatmann filter paper no.41. After appropriate dilutions with water it was analyzed spectrophotometrically at 273 nm (Shimadzu 1700, Japan). Drug content was calculated from the calibration curve of Aceclofenac in mixture of methanol and distilled water.

Saturation Solubility Studies

Solubility studies were carried out in distilled water according to the method reported by Higuchi and Connors [17]. Excess quantity of Aceclofenac and its formulations were introduced in 20 mL of distilled water and shaken for 24 hours at room temperature. The content of each flask was then filtered through a Whatmann filter paper. The filtrate was then diluted and assayed spectrophotometrically at 273 nm. Each solubility was determined in triplicate (n=3). The results obtained from saturation solubility studies were statistically analyzed.

Dissolution Studies

Dissolution studies were carried out using 0.1 N HCl in eight station USP type 1 dissolution (Model Disso 2000 tablet dissolution test apparatus, Lab India, India). The stirring speed used was 100 rpm and the temperature of the dissolution medium was maintained at 37± 0.5°C. The drug concentration in the dissolution medium was assayed spectrophotometrically at 273.5 nm. The results of dissolution studies were statistically validated.

Differential Scanning Calorimetry (DSC)

DSC patterns of formulations were compared with plain Aceclofenac and Chitosan. The DSC (pyris-6) thermograms were recorded at a heating of 10 ^{o}C/ min from 100^{o}C to 300^{o}C.

Powder Characteristics:

Angle of repose was determined by conventional funnel method. The blend was poured through a funnel fitted at appropriate distance from the base, till the blend achieves maximum cone height (h in cm) was obtained. Radius of the cone (r in cm) was measured, which is the average of 3 different radius of the heap circle and the angle of repose (q) was calculated using the formula:

$$q\ (^{\circ}) = \text{Tan-1}\ (h/r) \ldots . (1)$$

Angle of repose below 25° states a good flow property are always desired. Apparent bulk density (BD) was determined by pouring the weighed (W in g) amount of the blend into a graduated cylinder. The bulk volume (V in ml) of the blend was determined. The bulk density was calculated using the formula:

$$BD\ (gm/ml) = W/V \ldots . (2)$$

The tapped density (BD) was determined by pouring the weighed (W in g) amount of the blend into a graduated cylinder and the blend was tapped for a fixed time with uniform force. The final volume (Vf in ml) occupied in the cylinder was determined measured and the tapped density was calculated using the following formula:

$$TD\ (gm/ml) = W/\ Vf \ldots . (3)$$

The simplest way for measurement of free flow of powder is compressibility index, an indication of the ease with which a material can be induced to flow is given by compressibility index (CI) which is calculated as follows:

$$CI\ (\%) = 100 * (V\text{-}Vf/V). \ldots . (4)$$

Where, V (in ml) is the bulk volume and Vf (in ml) is tapped volume of the blend. The value below 15% indicates a powder with good flow characteristics.

Hausner's ratio (HR) is an indirect index of ease of powder flow, can be calculated by the following formula:

$$HR = TD/BD. \ldots . (5)$$

Where TD (in g/ml) is tapped density and BD (g/ml) is bulk density, lower Hausner's ratio below 1.2 indicates better flow properties of the blend.

Particle size determination

The particle size measurement was carried out using compound microscope (Micron OPTIK) on stage micrometer.

Statistical Analysis

The data were subjected to a multiple comparison test. Statistical significance was assessed using one-way analysis of variance (ANOVA) $P<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Determination of drug content

Percentage drug contents of prepared formulations were found to be in the range of 99.05 ± 0.42 w/w to 99.59 ± 0.92 w/w.

Saturation Solubility Studies

The results of saturation solubility are displayed in Table 1.

Table 1: Saturation solubility of pure Aceclofenac and its corresponding formulations with Chitosan and Chitosan chlorhydrate

System	Saturation solubility (mg / mL)*	Enhancement in solubility
A	0.0152±0.012	------
$ACH_{0.1}$	65.21 ± 0.23 [a]	5434.16
$ACH_{0.2}$	84.21± 0.54 [a]	5540.13
$ACH_{0.5}$	104.11±0.69 [a]	6849.34
$ACH_{1.0}$	89.86±0.65 [a]	5911.84
$ACHL_{0.1}$	86.74±0.21 [a]	5706.57
$ACHL_{0.2}$	96.35±0.45 [a]	6338.81
$ACHL_{0.5}$	129.23±0.24 [a]	8501.97
$ACHL_{1.0}$	101.84±0.72 [a]	8486.66

S.D.: Standard deviation; a significant difference compared to pure Aceclofenac i.e. significant ($p < 0.001$); Aceclofenac – A, Aceclofenac + Chitosan (0.1:1) - $ACH_{0.1}$, Aceclofenac + Chitosan (0.2:1) - $ACH_{0.2}$, Aceclofenac + Chitosan (0.5:1) - $ACH_{0.5}$, Aceclofenac + Chitosan (1:1) - $ACH_{1.0,}$ Aceclofenac + Chitosan chlorhydrate (0.1:1) - $ACHL_{0.1}$, Aceclofenac + Chitosan chlorhydrate (0.2:1) - $ACHL_{0.2}$, Aceclofenac + Chitosan chlorhydrate (0.5:1) - $ACHL_{0.5}$, Aceclofenac + Chitosan chlorhydrate (1:1) - $ACHL_{1.0}$

The solubility of Aceclofenac was found to be 0.0152 mg / mL [18]. The results of solubility depicted drastic improvement in solubility. The formulations of Aceclofenac showed 5434.16, 5540.13, 6849.34 and 5911.84 fold increase in solubility for 0.1, 0.2, 0.5 and 1 % ratios of Chitosan respectively. There was 5706.57, 6338.81, 8501.97 and 8486.66 fold increase in solubility for 0.1, 0.2, 0.5 and 1 % ratios of water soluble Chitosan with drug. It was observed that improvement in solubility was better with water soluble Chitosan as compared to Chitosan formulations. This might be reasoned as wetting property of water soluble Chitosan allowed more drug to go into the solution as compared to Chitosan [19]. All formulations with Chitosan as well as water soluble Chitosan reflected significant improvement in solubility as compared to pure drug ($p < 0.001$). However no significant difference was noticed within the formulations.

Table 2: The dissolution data of Aceclofenac and its corresponding formulations with Chitosan and Chitosan chlorhydrate in 0.1 N HCl at 37 ± 0.5°C

System	DP_5*± S.D.	DP_{15}*± S.D.	DE_5*± S.D.	DE_{15}*± S.D.
A	5.98±1.2	23.66±1.5	2.99±0.6	9.72±0.7
$ACH_{0.1}$	35.66±2.1[a]	66.33±2.6[a]	17.83±1.1[a]	38.34±1.3[a]
$ACH_{0.2}$	45.23±2.7[a]	80.21±2.8[a]	22.615±1.3[a]	46.88±1.4[a]
$ACH_{0.5}$	56.78±2.4[a]	100±1.6[a]	28.39±1.2[a]	65.44±0.8[a]
$ACH_{1.0}$	59.23±2.3[a]	78.25±3.1[a]	29.615±1.2[a]	55.85±1.6[a]
$ACHL_{0.1}$	12.36±2.1	46.32±2.3	6.18±1.1	23.92±1.2[a]
$ACHL_{0.2}$	23.25±2.7	89.24±2.7[a]	11.63±1.3[a]	40.82±1.9[a]
$ACHL_{0.5}$	42.11±2.4[a]	100±1.5[a]	21.06±1.2[a]	56.15±0.8[a]
$ACHL_{1.0}$	32.11±2.3[a]	86.33±3.0[a]	16.06±1.2[a]	42.83±1.5[a]

S.D.: Standard deviation; DP: % drug dissolved; DE: dissolution efficiency; a significant difference compared to pure Aceclofenac i.e. significant ($p < 0.001$); Aceclofenac – A, Aceclofenac + Chitosan (0.1:1) - $ACH_{0.1}$, Aceclofenac + Chitosan (0.2:1) - $ACH_{0.2}$, Aceclofenac + Chitosan (0.5:1) - $ACH_{0.5}$, Aceclofenac + Chitosan (1:1) - $ACH_{1.0}$, Aceclofenac + Chitosan chlorhydrate (0.1:1) - $ACHL_{0.1}$, Aceclofenac + Chitosan chlorhydrate (0.2:1) - $ACHL_{0.2}$, Aceclofenac + Chitosan chlorhydrate (0.5:1) - $ACHL_{0.5}$, Aceclofenac + Chitosan chlorhydrate (1:1) - $ACHL_{1.0}$

The reasons for improvement in solubility might be reduction in the size of pure drug. As the size reduced surface area as well as surface energy was increased. Increased surface energy could be responsible for better interaction with solvent and thus solubility was enhanced [20]. Another reason might be corresponded to use of Chitosan and water soluble Chitosan which was claimed to have surface wetting property thus responsible for better solubility [19].

Dissolution Studies

The percent drug release and dissolution efficiency values of pure drug and formulation are displayed in Table 2.

The dissolution curves of pure Aceclofenac and its formulation are shown in figure 2.

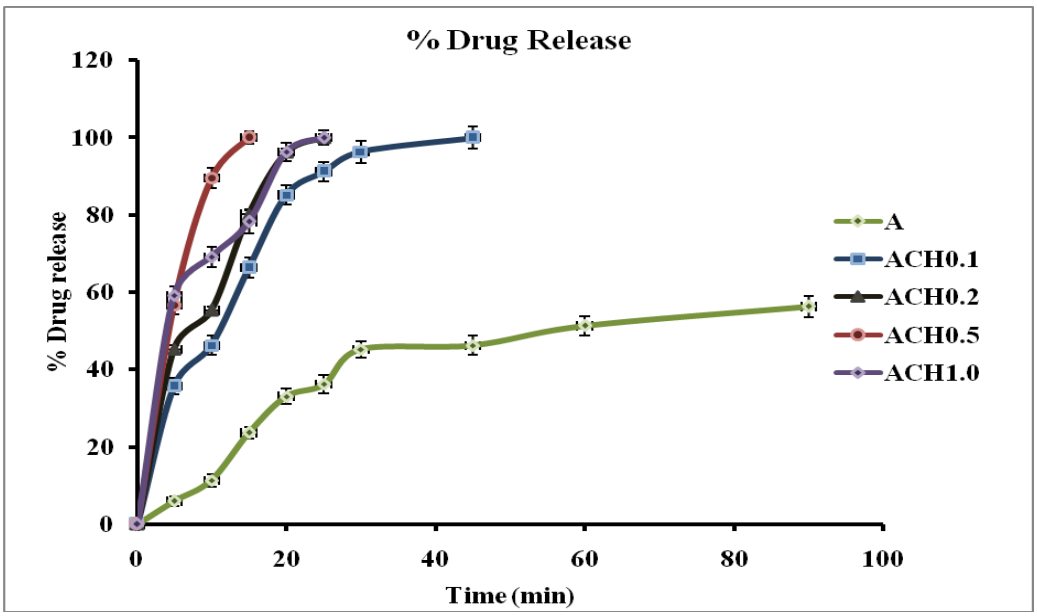

Figure 2a

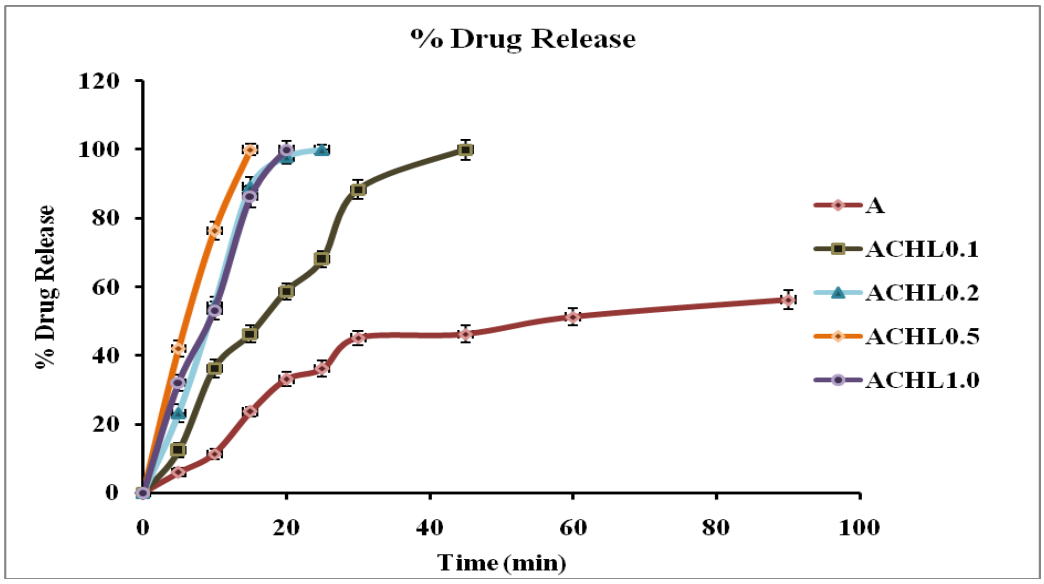

Figure 2b

Fig. 2: Dissolution curves of Aceclofenac and its corresponding formulations with Chitosan and Chitosan chlorhydrate

From the dissolution graphs it was reflected that dissolution of pure drug was incomplete in 90 minutes as Aceclofenac being poorly soluble in water. The microparticles of Aceclofenac with Chitosan depicted improved dissolution as compared to pure drug. The time taken for almost all formulations of Chitosan was less than 90 minutes. It might be due to reduction in particle size as compared to pure drug which increases the surface area available for further dissolution of drug. Surprisingly it was observed that $ACH_{1.0}$ takes more time for dissolution as compared to other ratios. This might be due to increased concentration of Chitosan hindered dissolution of drug.

The pattern of dissolution of Aceclofenac with Chitosan derivatives is shown in figure. The results confirmed improvement in dissolution as compared to pure drug. This reason might be suggested as use of water soluble Chitosan might have increased dissolution. Moreover as size was reduced, increased surface area might increase dissolution of formulations. During the experiment of dissolution it was observed that pure drug floated on the surface of dissolution media while all the formulations with Chitosan and derivatives of Chitosan immediately sank to the bottom as soon as entered into dissolution media. This effect might be attributed to better wetability of microparticles. [19]

Moreover, dissolution efficiency values calculated at 5 and 15 minutes for all formulation with Chitosan and all formulations with Chitosan derivatives indicated significant difference ($p < 0.001$) when compared to dissolution efficiency value of pure drug. The values for percent drug release and dissolution efficiency are displayed in table 2. All these results pointed towards significant improvement in dissolution of Aceclofenac. Thus the use of Chitosan and its derivatives, and added benefit of size reduction was responsible for improved dissolution pattern of Aceclofenac.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of Aceclofenac, Chitosan and formulations (0.5% formulations of Chitosan and water soluble Chitosan) are shown in Figure 3.

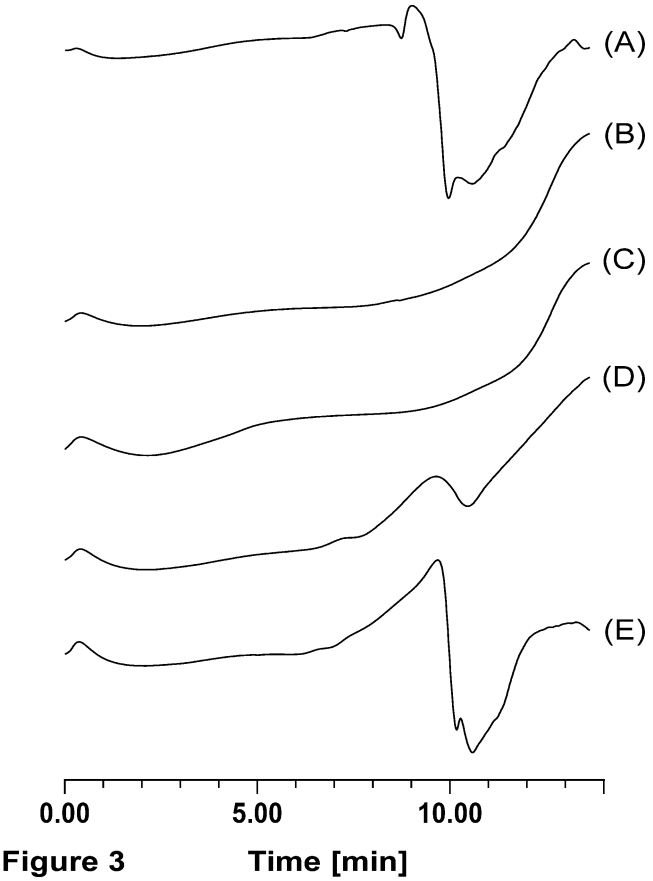

Fig. 3: DSC thermograms of pure Aceclofenac, Chitosan and its corresponding formulations with Chitosan and Chitosan chlorhydrate (0.5% Concentration)

DSC data helps in understanding the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations. As observed in the thermograms, Aceclofenac displayed a sharp endothermic peak at 158ºC indicating the melting point of the drug. As the sharp endotherm was seen in the thermogram of Aceclofenac it was clearly stated that the drug was in the crystalline form [21].

The DSC thermograms of Chitosan and water soluble Chitosan showed absence of any endotherm thus indicated its amorphous nature. Rather both Chitosan as well as water soluble Chitosan displayed Tg (glass transition temperature) in the range of 120 – 150 º C. The presence of Tg in the thermogram depicted amorphous nature of both Chitosan and its derivative [19].

In the thermogram of formulation (both of 0.5%) it was observed that endothems were broadened and Tg was increased. This might be contributed to decreasing crystallinity of Aceclofenac and some amount of Aceclofenac might have converted into amorphous state. Moreover increased Tg indicated complete dispersion of drug in the polymer and thereby might be responsible for better physicochemical properties. In addition to this as formulations thermogram showed broadened endothermic peaks indicating the polymer and drug compatibility [21].

Powder Characteristics:

The results of evaluation of powder characteristics are depicted in table no 3.

Table 3: Flow properties of Aceclofenac and its corresponding formulations with Chitosan and Chitosan chlorhydrate

System/Parameter	Bulk density (gm/cm)	Tapped density (gm/cm)	Angle of repose	Hausnar's Ratio*	Carr's Index (%)*
A	0.76	0.88	26.08	1.15	5.68
$ACH_{0.1}$	0.73	0.85	23.21	1.16	14.12
$ACH_{0.2}$	0.75	0.86	23.10	1.14	12.79
$ACH_{0.5}$	0.74	0.85	22.21	1.14	12.94
$ACH_{1.0}$	0.75	0.86	20.16	1.14	12.79
$ACHL_{0.1}$	0.75	0.85	22.12	1.13	11.76
$ACHL_{0.2}$	0.76	0.86	20.19	1.13	11.63
$ACHL_{0.5}$	0.77	0.86	18.13	1.11	10.46
$ACHL_{1.0}$	0.75	0.86	23.31	1.14	12.79

Aceclofenac – A, Aceclofenac + Chitosan (0.1:1) - $ACH_{0.1}$, Aceclofenac + Chitosan (0.2:1) - $ACH_{0.2}$, Aceclofenac + Chitosan (0.5:1) - $ACH_{0.5}$, Aceclofenac + Chitosan (1:1) - $ACH_{1.0,}$ Aceclofenac + Chitosan chlorhydrate (0.1:1) - $ACHL_{0.1}$, Aceclofenac + Chitosan chlorhydrate (0.2:1) - $ACHL_{0.2}$, Aceclofenac + Chitosan chlorhydrate (0.5:1) - $ACHL_{0.5}$, Aceclofenac + Chitosan chlorhydrate (1:1) - $ACHL_{1.0}$

Angle of repose of pure drug was found to be 26.08 indicating poor flow of drug from the funnel. The values of angle of repose of all formulations with Chitosan and Chitosan derivatives indicated lower values as compared to pure drug. But no significant difference was noted between drug and formulation with respect to angle of repose. The results pointed towards slight improvement in flow properties of formulation when compared to drug. A Carr's index is considered to be an indication of poor flowability when it is greater than 25, and below 15, it indicates good flowability [22]. When seen from the table Carr's index values were found in the range of good flowability range. This again confirmed slight improvement in flowability. Moreover The Hausner's ratio is used as an indication of the flowability of a powder [23]. The values of Hausner's ratio was found to be less than drug when compared with all formulations but it was not significantly reduced [24]. Thus all the results confirmed from angle of repose, Carr's index and Hausner's ratio displayed slight improvement in powder characteristics of formulation than pure drug. The reason for slight improvement in flow properties of microparticles could be due to spherical shape of microparticles. Generally particles with reduced size have shown poor micromeritic properties due to their higher surface charge. But the spherical shape of microparticles might be responsible for good flow properties as spherical particles of formulations didn't hider flow of drug through funnel while that of rough shape of pure drug particle might put obstacle in the flow of drug through funnel [25,26].

Particle size determination

Particle size of pure drug and prepared microparticles was checked by using compound microscope [27]. The size of pure Aceclofenac was found to be 25.31µm while that of Aceclofenac microparticles with Chitosan was found in the range of 9.5 to 14 µm size increasing with increasing concentration. The Aceclofenac microparticles with Chitosan derivatives also found to be reduced in size ranging from 8.2 to 13µm. It was observed that with increasing concentration particle size was increased. Thus lower concentration might be useful for reduced particle size.

CONCLUSION

Microparticles of Aceclofenac prepared with Chitosan and water soluble Chitosan displayed drastic improvement in both solubility as well as dissolution properties. Among the ratios used Chitosan used in 0.5% concentration gave best results. In addition to that results were better for water soluble Chitosan when compared to Chitosan. Thus Chitosan and water soluble Chitosan used in optimum concentration could be applied for improving solubility and dissolution. Moreover formulations depicted better micromeritic properties. Thus Chitosan and its derivative could be helpful to improve the flow properties of Aceclofenac and in turn it would avoid further processing steps like mixing, granulation in preparation of directly compressible tablets.

ACKNOWLEDGEMENTS

Authors are grateful to Mahatani Chitosan, Ahmedabad for providing gift sample of Chitosan for research work. The authors express sincere thanks to Cipla Mumbai, India for providing gift sample of drug. The authors are thankful to Government College of Pharmacy. Aurangabad, Maharashtra, India for providing DSC facility. Authors are very much thankful to Principal, Govt. College of Pharmacy, Karad, and Maharashtra, India for providing laboratory facilities and constant encouragement.

REFERENCES

1. Brahmankar DM, Sunil B. Jaiswal. Biopharmaceutics and Pharmacokinetics a treatise.2nd ed. Vallabh Prakashan (New Delhi) 2009.
2. Zhang JY, Shen ZG, Zhonga J, Hub TT, Chena JF, Mac ZQ, Yun J. Preparation of amorphous cefuroxime axetil nanoparticles by controlled nanoprecipitation method without surfactants. International Journal of Pharmaceutics. 2006; 323: 153–160.
3. Mosharrafand M, C Nystr¨om. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. International Journal of Pharmaceutics. 1995; 122: 35–47.
4. Abu T.M. Serajuddin. Saltformation to improve drug solubility. Advanced Drug Delivery Reviews 2007; 59: 603–616.
5. Dixit M, Kini AG, Kulkarni PK. Enhancing the dissolution of polymorphs i and ii of mefenamic acid by spray drying. Turkey Journal of Pharmaceutical Sciences, 2012; 9 (1): 13-26.
6. Ruan LP, Yu BY , Fu GM, Zhu D. Improving the solubility of ampelopsin by solid dispersions and inclusion complexes. Journal of Pharmaceutical and Biomedical Analysis 2005; 38: 457–464.
7. Pandit V, Gorantla R, Devi K, Pai RS, and Sarasija S. Preparation and Characterization of Pioglitazone Cyclodextrin Inclusion Complexes. Journal of Young Pharmacists. 2011 O; 3(4): 267–274.
8. Bansal K, Pant P, Rama P, Rao T, Padhee K, Sathapathy A and kochhar PS. Micronization and dissolution enhancement of Norethindrone. International Journal of Research in Pharmacy and Chemistry, 2011, 1(3), 315-319
9. Patel VR and Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. Journal of Advanced Pharmaceutical Technology & Research. 2011; 2(2): 81–87.
10. Prasad RV, Rakesh MG, Jyotsna RM, Mangesh ST, Anita PS and Mayur PK. Pharmaceutical Cocrystallization : A Review. International Journal of Pharmaceutical and Chemical Sciences. 2012; 1 (3): 725-736
11. Yadav VB, Yadav AV. Enhancement of solubility and dissolution rate of indomethacin with different polymers by compaction process. International Journal of Chemical Technology and Research. 2009; 1(4): 1072-1078
12. Joint publication of the British Medical Association and the Royal Pharmaceutical Society; British National Formulary 55, (London) 2008; 537.
13. Setty CM, Prasad DVK, Gupta VRM, and B. SA. Development of fast dispersible Aceclofenac tablets: Effects of functionality of superdisintegrants. Indian Journal of Pharmaceutical Sciences, 2008; 70(2):180-185.
14. Martindale – The Complete Drug Reference, 33rd Edition, Edited by Sean C Sweetman, Published by Pharmaceutical Press, UK, 2002; 11, 63.
15. Aleem MA, Dehghan MH and Babu VR. Solid dispersion- an approach to enhance the dissolution rate of Aceclofenac by

using 32 factorial design. International Journal of Pharmaceutical Sciences and Research, 2010; 1 (12): 203-208

16. Shaji J, Jain V, Lodha S. Chitosan: A Novel Pharmaceutical Excipient. International Journal of Pharmaceutical and Applied Sciences. 2010; 1 (1): 11-28.
17. Higuchi T., Connors K.A., Phase solubility techniques, Advances in Analytical Chemistry and Instrumentation.1965, 4, 117 – 212.
18. Shakeel F, Ramadan W, Shafiq S. Solubility and Dissolution Improvement of Aceclofenac using Different Nanocarriers. Journal of Bioequivalence & Bioavailability.2009; 1: 039-043.
19. Kini AG, Dixit M, Kulkarni PK**.** Enhancement of solubility and dissolution rate of poorly water soluble drug by spray drying using different grade of Chitosan. International Journal of Pharmacy and Pharmaceutical Sciences. 3, (Suppl 2), 2011;
20. Khan F, Katara R, Ramteke S. Enhancement of Bioavailability of Cefpodoxime Proxetil Using Different Polymeric Microparticles. AAPS PharmSciTech. 2010; 11(3): 1368–1375.
21. Uma Devi SK, Thiruganesh R and Suresh S. Preparation and characterization of pectin pellets of Aceclofenac for colon targeted drug delivery. Journal of Chemical and Pharmaceutical Research. 2010; 2(1): 361-374.
22. Kanig, Joseph L.; Lachman, Leon; Lieberman, Herbert A. The Theory and Practice of Industrial Pharmacy 3rd ed. Lea & Febiger (Philadelphia) 1986.
23. Grey RO and Beddow JK. On the Hausner Ratio and its relationship to some properties of metal powders. Powder Technology. 1969; 2(6): 323-326.
24. Kawashima Y, Ima M, Takeuchi H, Yamamoto H, Kamiya K, Hino T. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tabletting designed by spherical crystallization process. Powder Technology 2003; 130: 283-9.
25. Yadav AA, Yadav DS, Karekar PS, Pore YV, Gajare PS. Enhanced solubility and dissolution rate of Olmesartan medoxomil using crystallo-co-agglomeration technique. Der Pharmacia Sinica, 2012; 3 (2):160-169.
26. Choudhary NH, Kumbhar MS, Dighe DA, Mujgond PS, Singh MC, Solubility Enhancement Of Escitalopram Oxalate Using Hydrotrope. International Journal of Pharmacy and Pharmaceutical Sciences, 5, 1, 2013; 121-125.
27. Chaudhari MD, Sonawane RO, Zawar LT, Nayak S, Bari SB; Solubility And Dissolution Enhancement Of Poorly Water Soluble Glimepiride By Using Solid Dispersion Technique International Journal of Pharmacy and Pharmaceutical Sciences 4, (Suppl 5), 2012; 534-539.