Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6 suppl 2, 2014

Research Article

DEVELOPMENT AND CHARACTERIZATION OF CO-GROUND MIXTURES AND SOLID DISPERSIONS OF ARIPIPRAZOLE WITH HYDROPHILIC CARRIERS

MUNEERA BEGAM[1], VISHNU DATTA M[2], D V GOWDA*[2], ARAVINDARAM A.S[3], SIDDARAMIAH[4]

[1]Department of Chemistry, Sri Jayachamarajendra College of Engineering, Mysore - 570 006, [2]Department of Pharmaceutics, JSS College of Pharmacy, JSS University, S S Nagar, Mysore 570015, [3]Farooqia College of pharmacy, Farooqia Educational Complex, Farooqia Road, Eidgah, Tilak Nagar, Mysore – 570021, [4]Department of Polymer Science & Technology, Sri Jayachamarajendra College of Engineering, Mysore - 570 006, India Email: dvgowda@jssuni.edu.in

Received: 10 Dec 2013, Revised and Accepted: 09 Feb 2014

ABSTRACT

Objective: The aim of the present work was to improve the dissolution of poorly water-soluble drug Aripiprazole (ARP) and to understand the effect hydrophilic carriers [guar gum(GG), modified guar gum (MGG), and hydroxypropyl methylcellulose (HPMC)]on drug solubility.

Methods: Physical Mixture (PM), ground mixtures (GM) and solid dispersions (SD) were prepared by simple mixing, metal ball mill (MBM) and solvent evaporation method, respectively.

Results: The solubility of ARP in simulated gastric fluid and simulated intestinal fluid at 37^0 C was found to be 76.78 µg/mL and 291µg/mL, respectively. Grinding time affects the dissolution rate was observed. Ground mixture develops more fine particles and show less friability index than physical mixture and solid dispersion. FTIR studies reveals no chemical interaction between drug and carriers. The carriers showed the wettability of the ground products in the order MGG > GG >HPMC. The order of dissolution rate enhancement of the different hydrophilic carriers was in the order of MGG>GG>HPMC. GM containing MGM showed better dissolution than SD and PM.

Conclusion: From the study it was concluded that grinded ARP with hydrophilic carriers improved the dissolution rate not only due to particle size reduction, but also resulted from the ability of these carriers to prevent aggregation of the finely divided drug particles, to improve wettability and to inhibit recrystallization during dissolution.

Keywords: Co-ground mixtures; Dissolution rate enhancement; Hydrophilic carriers; Aripiprazole; Poorly water soluble drug.

INTRODUCTION

Solid dispersions, which are generally prepared by melting or solvent methods, possess several challenges [1].Finely dispersed drug particles in solid dispersion systems are usually in the thermodynamically unstable amorphous form [2]. This could lead to crystallization upon storage, especially under humid conditions, resulting in changes in drug dissolution/bioavailability [3]. Problems of the melting technique are that there is a possibility of thermal drug degradation. The solvent methods suffer from the undesirable environmental impact of many organic solvents and their potential toxic and carcinogenic effects [4].

Poor biopharmaceutical properties are greatest challenges to the therapeutic efficacy of the potent drug. Micronization of drug powders results in a considerable decrease of particle size. However, the products tend to agglomerate, which leads to a considerable reduction of specific surface area and formation of a cohesive powder with poor flow properties [5, 6]. Co-grinding of poorly soluble drugs with hydrophilic carriers is an interesting technique for the production of micronized and stable drug particles. Many authors have reported on the use of this method for the enhancement of dissolution rates of various drugs. Examples include Aceclofenac and Neusilin [7] Indomethacin, Furosemide and Naproxen [8]. Amorphous solid dispersion solution exhibits improvement in wettability of drug as well as decreases in the particle size of the drug to the molecular level, if the carriers are easily wetted [9].Availability of more surface area helps for easy mass transfer and showed increased dissolution rate according to modified Noyes Whitney equation [10]. Additionally less enthalpy require to separate drug molecule from carrier molecules or each other, compared to the energy required to separate drug molecules within a crystalline structure. When the Gibb's free energy of dissolution decreases and amorphous drugs enhanced solubility [11]. Some of the amorphous drugs mix with small quantities of plasticizer (water), they tend to revert to the crystalline state [12]. Aripiprazole, 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl] butoxy]-3, 4 dihydro- 2 – (1H) quinolinone, (APZ) is a second generation antipsychotic drug indicated for the treatment of schizophrenia and related psychoses[13]. It is a weakly basic drug (pKa= 3. 55), poorly water soluble, is usually supplied as crystals having a melting range of 136-138°C , low and irregular bioavailability following oral administration of APZ was reported [14].Two meta stable polymorphs as well as four different solvates crystallized forms were reported from more than 20 patent applications [15]. The objective of the present study was to improve the dissolution of poorly water soluble drug ARP using cogrinding techniques and SD with pharmaceutically acceptable above mentioned carriers.

MATERIALS AND METHODS

Materials

Aripiprazole, Gift sample from Pfizer, India). Guar gum I.P., Hydroxypropyl methylcellulose (HPMC, Methocel®K15M) and other materials supplied by the S.D fine chemicals Mumbai, India.

Preparation of Physical Mixture (PM), Ground Mixtures (GM) and solid dispersions (SD)

APZ and with each carrier (GG, MGG&HPMC of different ratio- Table 1) was grounded using metal ball mill (MBM). The MBM consisted of a 40 ml jar and eight metal balls with 10 ml jar and cooling attachment. Test samples were ground at 70 rpm for 30, 60, or 120 min at ambient conditions. Physical mixtures of APZ were prepared by mixing APZ with the hydrophilic carriers for 5 min in 100 mL bottles, until a homogeneous mixture was obtained. The resulting mixtures were sieved and the 120-500 µm particle sizes were obtained using 30 and 120 mesh screen. The powders were stored in a screw cap vials at room temperature until use.

Solid dispersions were prepared using ARP with GG,MGG and HPMC in the ratios of 1:3, 1:6 &1:9, respectively.APZ was dissolved separately in a minimal volume of ethanol and GG, MGG and HPMC in distilled water, separately. The ARP contain ethanolic solution was then poured into aqueous solution of carriers under continuous stirring. The mixture was heated in a water bath (70^oC) under vacuum and vigorous stirring. Initially a transparent mass translucent viscous mass was observed and finally a pale yellow moist mass was produced. The moist mass was transferred to a

vacuum desiccators with heating device and kept at 70° C for2h and 40° C overnight. The solid mass was ground and particle size fraction of 125- 500µm was obtained by sieving and kept in a screw capped glass vial until use.

Solubility measurement of ARP

Excess amount of ARP was weighed into test bottles to which 10ml of dissolution medium containing various concentrations of carriers was added & samples were sonicated (Metler Electronics model ME5.5, USA) for 2 h at room temperature and filtered through a 0.22 µm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 254 nm (Shimadzu 120, Japan).

Contact Angle Measurements

The mixtures were compressed to flat-faced pellets were placed onto an adjustable platform of the contact angle goniometer (Kruss G1 goniometer, Hamberg, Germany). Using a micro- syringe, 2 µl distilled water was applied onto the mixtures. The angles were measured 30 seconds after wetting the samples (n= 3).

Friability study

The friability of agglomerates developed from physical mixture, ground mixture and solid dispersion was determined. The friability index (F1) was determined using Rubinstein [16] Eq. as a function of time.

$$F1 = (d_g)_t/(d_g)_n \times 100 (1)$$

$(d_g)_t$= mean geometric diameter after time t, $(d_g)_n$ = initial geometric diameter

Determination of drug content

100 mg physical mixture, ground mixture & solid dispersions (individually) were dissolved in 100 ml of methanol. The resulted solution was analyzed spectrophotometrically at 254 nm after suitable dilution.

Scanning Electron Microscopy (SEM) and Internal pore structure

The shape and surface characteristics were determined by scanning electron microscopy (model-LV 5600, Jeol, USA) and photomicrographs were recorded. To determine the internal pore structure of the particles, computed tomography CT scanner (Phoenixn nanotom-M, GE-India) was used. Combining the data of the maximum inscribed diameter (d_{max}) and the equivalent diameter (d_e) provides information about the structure of the pores.

Differential Scanning Calorimetry (DSC)

DSC studies (Du Pont thermal analyzer with 2010 DSC module) were carried out. The DSC scans of the samples were recorded in nitrogen atmosphere at a heating rate of 10 °C/min.

Fourier transform- infrared spectroscopic analysis (FT- IR)

FTIR spectra(Shimadzu, Model 8400S, Japan) of pure drug, physical mixture, ground mixture & solid dispersions (with and without drug) were obtained using KBr pellet method (applying pressure of 6000 kg/cm^2

Powder X-Ray Diffractometry

X-ray diffraction patterns of Pure drug, pure drug, physical mixture, ground mixture & solid dispersions (with and without drug) were recorded using (Phillips PW 1710, Tokyo, Japan) X-ray diffractometer with a copper target, voltage 40 Kv, current 30 MA at a scanning speed of 0.30 °C/min.

Dissolution Studies

Hand filled, hard gelatin capsules of the formulations, containing 20mg of drug, were used for the dissolution studies. USP XXI dissolution apparatus, type II. 900 ml dissolution medium and drug release was studied (2 h in pH 1.2, and 22 h in pH 7.2,) at 100 rpm using at a temperature of 37 ± 0.5 °C. 10 ml of samples were withdrawn periodically and after appropriate dilution estimated for ARP concentration spectrphotometrically at 274 nm. The release data was analyzed using PCP dissolution - V2 – 08 and Graph Pad Instat software.

To study the drug release behavior from polymeric systems more than one type of release phenomenon is involved [17]

$$M_t/M_f = k.t_n (2)$$

Where Mt / Mf is the drug released fraction at time t, k is a constant incorporating the structural and geometric. The dissolution profile of all the batches was fitted to first order [18],Higuchi [19], Hixon-Crowell [20], Korsemeyer [17] and Peppas [17] and Bekker and Lonsdale [22] to ascertain the kinetic modeling of drug release.

A differential factor (f_1) and similarity factor (f_2) were calculated from dissolution data according to the following equations

$$f_1 = \frac{\sum_{t=1}^{n}[R_t - T_t]}{\sum_{t=1}^{n} R_t} \times 100 (3)$$

$$f_2 = 50 \log\{[1 + (\frac{1}{n}) \sum_{t=1}^{n}(R_t - T_t)]^{-0.5} \times 100\}(4)$$

where, f_1 - differential factor, f_2 - similarity factor, n – number of time point, R_t– dissolution value of the reference at time, 't' and T_t - dissolution value of test formulation at time 't'. Differential factor, f_1 was calculated by the percentage difference between the two curves at each time point and measured the relative error between the two curves. The acceptable range for differential factor, f_1 is 0-15. If dissolution profile to be considered similar, the values for $f_2$should be in the range 50 - 100.

Stability of the prepared co-ground mixtures

Optimized formulations were subjected for stability studies at 25 ºC/60% RH, 30 ºC/65% RH, 40 ºC/75% RH for 90 days and the above formulations were evaluated for drug content.

Table 1: Different ARP formulations with carriers

Code	PM formulations (Drug: Polymer)	Code	GMformulations (Drug: Polymer)	Code	SD formulations (Drug: Polymer)
A1	ARP:GG (1:1)	B1	ARP:GG (1:1)	C1	ARP:GG (1:1)
A2	ARP:GG (1:3)	B2	ARP:GG (1:3)	C2	ARP:GG (1:3)
A3	ARP:GG (1:6)	B3	ARP:GG (1:6)	C3	ARP:GG (1:6)
A4	ARP:MGG (1:1)	B4	ARP:MGG (1:1)	C4	ARP:MGG (1:1)
A5	ARP:MGG (1:3)	B5	ARP:MGG (1:3)	C5	ARP:MGG (1:3)
A6	ARP:MGG (1:6)	B6	ARP:MGG (1:6)	C6	ARP:MGG (1:6)
A7	ARP:HPMC (1:1)	B7	ARP:HPMC (1:1)	C7	ARP:HPMC (1:1)
A8	ARP:HPMC (1:3)	B8	ARP:HPMC (1:3)	C8	ARP:HPMC (1:3)
A9	ARP:HPMC (1:6)	B9	ARP:HPMC (1:6)	C9	ARP:HPMC (1:6)

RESULTS AND DISCUSSIONS

Evidence have shown in the recent years that hydrophilic carriers have the physical properties and behavior suitable to prepare grinding mixture. Grinding is a relatively simple and effective method to prepare a drug delivery system with an enhanced dissolution rate.

Solubility studies

The solubility of crystalline ARP,A6, B6 & C6 in simulated gastric fluid and simulated intestinal fluid at 37^0 C was found to be 76.78,107.23,198.23, 182.98µg/mL and 291.87, 303.45,464.12, 334.2587µg/mL, respectively. Solubility of ARP fromB6 has been significantly higher than pure drug, A6,and C6 (Table 2), due to decreased sizes of individual crystals.MGG with ARP (1:6) by GM showed better solubility than GG, HPMC. Because constituent crystals decreased with increase during grinding time. The values of angle of repose (θ) for the particles produced from ground mixture were in the range of 19.65 - 21.53 (Table 2), indicating excellent flow property than solid dispersion. Physical mixture exhibits passable and pure drug showed poor flow property, due to dumbbell shaped particles with protruding surfaces (Fig. 1b).From the above result it was observed that ground mixture was more effective than solid dispersion and physical mixture

Table 2: Various parameters of mixture from Physical mixture,Ground mixture, solid dispersion

Formulations	Solubility, µg/mL		Surface area m^2/g	Angle of repose, θ	Average diameter, µm	Friability index (for 5 min)	Drug content, % w/w
	Gastric fluid	Intestinal fluid					
Pure ARP	76.78 ±1.2	191.87±1.1	0.65± 0.8	39.65±1.5	34.67± 10.98	91.54± 0.07	99.82 ± 1.27
A3	83.12 ± 0.9	223.12±1.2	0.92± 0.7	32.54±1.9	23.56±11.65	89.67± 0.08	97.01± 1.68
A6	97.23 ± 1.1	276.89±1.4	1.00 ±0.5	34.78±1.6	22.87± 9.8	86.78± 0.05	97.18± 1.26
A9	107.23±1.3	303.45±1.4	1.02±0.3	36.65±1.8	21.87± 6.7	85.45± 0.03	96.89± 1.67
B3	123.23±1.4	367.23±1.6	1.05±0.7	19.65±1.6	18.67± 3.2	81.38± 0.09	98.76± 1.29
B6	167.98±1.02	407.34±1.7	1.18±0.8	20.67±1.7	16.12± 6.9	78.67± 0.08	98.89 ± 1.08
B9	198.23±1.1	464.12±1.6	1.03±0.9	21.53±1.8	19.32± 7.6.	74.32± 0.05	98.72± 1.25
C3	96.54±1.2	243.12±1.8	1.01±0.3	29.23±1.5	22.54±9.8	82.12± 0.02	97.67± 1.12
C6	113.21±1.3	294.34±1.9	1.02±0.6	28.65±1.8	20.87± 4.6	81.34± 0.03	97.76± 1.32
C9	182.98±1.6	334.25±1.3	1.01±0.4	29.37±1.4	21.67± 5.3	80.76± 0.02	97.85±1.140

n= 3

Contact Angle Measurements

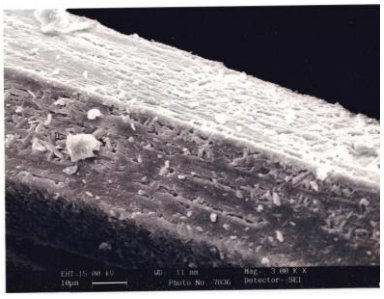
Contact angle was measured, 19º for A6,27º B6&32º C6 ,compared to 51ºfor the untreated ARP particles. It was observed that ground mixture, showed decreased particle size and increased surface area than physical mixture &solid dispersion.MGG exhibited better wettability than GG &HPMC.

Determination of drug content

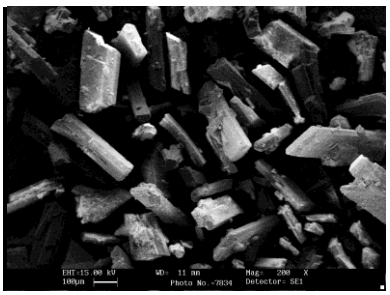
Drug content for the physical mixture, ground mixture and solid dispersion presented in the Table 2. Drug content in all the formulations were in the range of 98.89 to 97.01% w/w. Drug content was least in formulation A3 (97.01 % w/w) and high for formulation B6 (98.89 % w/w). Interestingly drug content increases with increased carrier ration in mixture. This might be due to increased relative surface area of the particles leads to more drug content.

Friability study

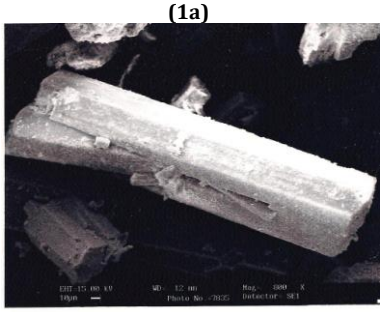
Ground mixture containing MGG produces fine particles & percentage of the large particles not more than 10% w/w. Particles developed from ground mixture (1.19 ± 0.5m^2/g) have shown more specific area than physical mixture (0.93 ± 0.3m^2/g) and solid dispersion (0.85 ± 0.4m^2/g), whereas pure drug has specific surface area 0.35± 0.8m^2/g (Table 2). From the above result grinding method and time exhibit a significant effect on the significant change in the surface area of the agglomerates [23].



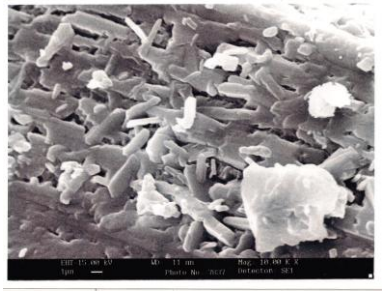
(1a)



(1b)



(1c)



(1d)

Fig. 1: SEM photomicrographs of; (1a) pure crystalline drug (1b) Fractured agglomerates (1c) Crystalline drug in the form of needles and has rough surface, (1d) Agglomerates has shown tube like structure and sintered crystals

Scanning Electron Microscopy (SEM)

SEM photomicrograph of the crystalline drug as such and mixture produced from ground mixture and physical mixture methods also solid dispersions as shown in Fig. (A) and 1(b). The crystalline drug {Fig. 1(c)} is in the form of needles and has rough surface. Ground mixture and solid dispersion resulted in some changes such as development of cracks in the crystals, reduction in particle size and surface roughness. But physical mixture resulted in particle size reduction, irregular in shape having rough surface. Particles produced from ground mixture and solid dispersion, regular in shape having smooth surface with pores. It was observed that some of the size reduced particles have shown tube like structure and sintered crystals {Fig. 1(d)}.The tubular structures formed due to applied shear during the process. Along with tubes, some plates and fine particulate matter was also observed. The tubular structures when analyzed at higher magnification have shown bends at different places. The broken tube showed an opening, which revealed the formations of channels. The hallow tube opening may be clearly observed in the fractured particles. The average diameter was found to be 21.87 µm with pore diameter 4.9 µm for A9 (physical mixture), 15.32 µm with pore diameter 2.9 µm for B9 (Ground mixture), 19.67 µm with pore diameter 3.6 µm for C9 (solid dispersion). Applied energy to the drug crystal is responsible for occurrence of significantly different crystal structures such as hollow tubes and plates.

Differential Scanning Calorimetry (DSC)

DSC thermo grams of the pure drug, mixture obtained from physical mixture (A9), ground mixture (B9) and solid dispersion (C9)presented in Fig.2.Samples A9 (142.36^{0}C), B9(142.36^{0}C), C9 (141.75^{0}C) showed relatively broad melting endothermic peak and pure drug exhibits sharp endothermic peak at 140.43 ° C. The peak intensity corresponding to the melting of ARP decreased in the thermo grams of physical, ground mixture and solid dispersions. These results indicate that only a small fraction of the drug substance existed in the crystalline state. Reduction in the melting point and enthalpy of the melting endotherm was observed in the physical, ground mixture and solid dispersions. Small sized particles leads to high surface energy, which creates an energetically suboptimal state causing a decrease in the melting point [24].

The changes in the melting point due to lattice defects created during grinding [25]. The slow decrease in heat capacity may be due to the defects in crystalline structure.

Fourier transform- infrared spectroscopic analysis (FT- IR)

From the FTIR studies (Fig.3), the characteristic bands for important functional group of pure drug, mixture obtained from physical mixture (A6), ground mixture (B6) and solid dispersion (C6)were identified. It was observed that 3500.0 cm^{-1}due to N-H stretching, 3192.6 cm^{-1}due to Ar-H stretching 2946.7 cm^{-1} due to C - H stretching, 1681.6 cm^{-1}due to C -O stretching, 1577.3 cm^{-1}due to C - O stretching, 1446.5 cm^{-1}due to C -H stretching, 1272.8 cm^{-1}due to C – O - C stretching and 862.6 cm^{-1}due to O - C - H stretching. FTIR spectra showed that the characteristics bands of ARP were not altered without any change in their position, indicating no chemical interactions between the drug and polymers used. A comparison and interpretation of this region in our spectra agrees with their conclusions [26].

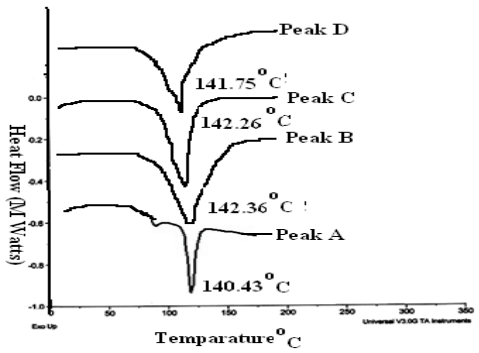


Fig. 2: DSC thermo grams of ARP= peak A, A6 = peak B, B6 = peak C&C6 = peak D

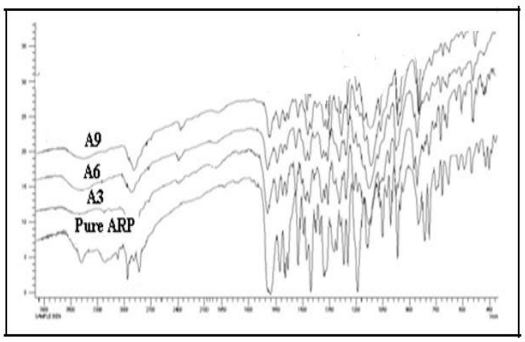


Fig. 3: FTIR spectra of Pure ARP, A3,A6,A9, B3, B6, B9, C3, C6, C9

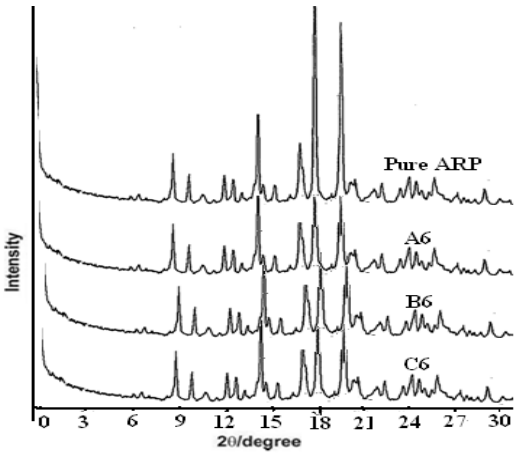


Fig. 4: X-ray powder diffraction patterns of pure ARP, physical mixture (A6), Ground mixture (B6), Solid dispersion (C6)

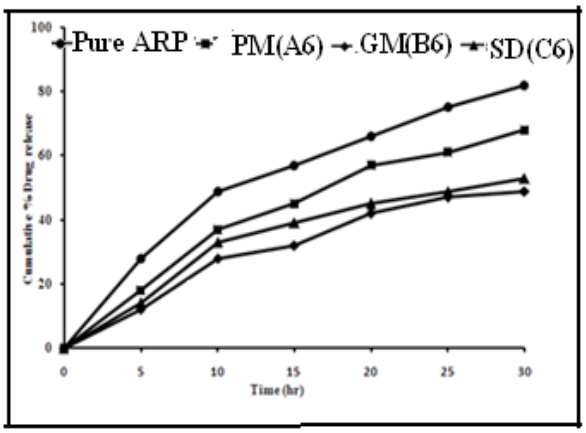


Fig. 5: Dissolution profiles of Pure crystalline ARP, GM, SD and PM

X ray powder diffraction (XRPD) spectrum of Aripiprazole

Crystalline nature of ARP was indicated by the presence of multiple sharp peaks (Fig.4). The powder diffractograms allow a clear and fast identification of the ARP, especially by the peaks between 2° and 27° 2θ, respectively. X-ray diffraction patterns of ground mixtures of ARP with GG, MGG, and HPMC indicated the characteristic peaks of ARP were of significantly lower intensity. Garekani [27] et al have reported that decrease in the intensity to the changes in crystal habit of drug. ARP existed in a less crystalline state in the ground mixtures with GG and MGG compared to the corresponding physical mixtures. On the contrary, a halo diffraction pattern was obtained with HPMC. Small peaks were observed for fine ground drug particles & X-ray diffractograms of pure ARP showed principal peak at 19.87° and intense peaks at3.89°, 8.48°, 12.22°, 17.32°, 19.69°, 21.39°, 24.84°. ARP contain mixtures(A6, B6, C6) showed intense peaks at 3.95°, 8.58°, 12.85°,17.65°, 19.85°, 21.45°, 24.89° as presented in Fig.4. There was a significant decreases in the intensities of the peaks in the region of lower 2θvalues (up to 18.22°), whereas peaks in the region above 2θvalues (25°) have been broadened. There was no change observed in the d – spacing values of various samples. The broad and asymmetric endotherm in DSC thermo grams and significantly shifts in the XRD patterns may be attributed to this wide variety of crystalline structures. As observed in SEM these include plates and tubes along with fine drug crystallites and some sintered crystals, formed during grinding. The defects in the crystal structure produced due to ultrasonic energy may be responsible for these changes and also changes in the melting point due to lattice defects created during grinding and melt quenching [28]. The slow decrease in heat capacity may be due to defects in crystalline structure. Powder diffractigrams revealed the crystalline nature of pure ARP&ARP showed number of sharp and intense peaks. This may be attributed to the incorporation of ARP between parts of the crystal lattice of the MGG, leading to a change in the degree of crystallinity of the ARP [29].

Dissolution Studies

Dissolution profiles of pure crystalline ARP and PM (A6), GM(B6) and SD(C6) was shown in Fig.5 Release of the ARP from the PM was significantly slower than from the corresponding GM(B6) because of the lower crystallinity of ARP and the weak interparticular bonding with the carrier. Mixtures ground with the MGG showed faster drug release profiles than mixture ground with the GG and HPMC. The dissolution rate of the ARP from GM (A6) was higher than SD (C6). MGG resulted in an improved dissolution rate when compared to SD and PM mixture prepared with MGG.

Pure ARP PM(A6) GM(B6) SD(C6)

It was observed that the dissolution rate increased with increased grinding time (up to 30 min using 50 rpm), but increased grinding time (more than 30 min using 50 rpm)resulting in a decreased drug release due to produced finest particle exhibits increased surface free energy and aggregation of particles because of electro statically charged particles. A satisfactory dissolution rate and minimal heat stress were thereforeobtained with ground mixtures with a grinding time of 30 min using 50 rpm. The rank order of dissolution rate enhancement of the different hydrophilic carriers was in the order of MGG>GG>HPMC.Ground mixtures with MGG as higher dissolution rate due to decreased particle size, thus increased surface area, and the improved wettability reflected by a contact angle of only 19º when compared to 51º of the untreated ARP particles. The enhanced drug dissolution rate from ground mixtures with MGG by improved wettability&solubilization effects. A possible stronger solubilization effect could operate in the diffusion layer immediately surrounding the drug particles in the early stages of the dissolution since the carrier rapidly dissolved completely.In addition, HPMC could inhibit the recrystallization of the partially amorphous drug in the dissolution fluid immediately after starting of the dissolution test[30].

ARP has severe problem of sticking to the punches. The compressibility describes the reduction of volume in the die at applied punch pressure. The compressibility was studied using the Heckel equation. Pure crystalline drug could not be compressed and has capping and sticking problems. Therefore Heckel plot was carried out only on the GM containing MGG. It was observed that mean yield pressure required for GM containing MGG22.54kg/cm^2, at which stable compact could be obtained. Sticking was not observed for GM containing MGG samples during compression of samples. The difference in the compressional properties of the pure crystalline drug and GM containing MGG samples may be attributed to properties of crystals. It was observed that better compressibility of plate type crystal of ARP as compared to needle shaped. Surface roughness of the needles makes it prone to sticking was observed[31].But needle type crystals with reduced surface roughness as obtained by grinding of pure crystalline drug in suspension also showed sticking problems. The SEM photographs of tablet surface obtained using pure crystalline drug. From SEM photographs it revealed that crystalline drug tablet has rough surface with large cracks between due to sticking whereas surface of GM containing MGG tablet was smooth and devoid of any cracks indicating non sticking nature. Therefore non sticking characteristics of GM containing MGGmay be attributed to change in crystal habit and suitable for direct tableting with addition of small amount of excipient.

Obtained 'n' values (Table 3) for all the formulations ranged from 0.4234 to0.4814, indicating that the release mechanism was non-Fickian &. Drug release was dependent on both drug diffusion and polymer relaxation. Diffusion depending on the size and wettability of the particles. As gradient varies, the drug is released and the distance for diffusion increases[32].Obtained correlation coefficient, R^2 for A6, B6 & C6lies in the range of 0.981 – 0.997. It was observed that drug releases by diffusion was more than the polymer relaxation as the values of n were nearer to 0.5.The differential factor (f_1) for formulationsA6 (9.34), B6 (9.12) & C6 (9.12)and similarity factor (f_2) formulationsA6 (74.23), B6 (69.132 & C6 (71.65)obtained, respectively from dissolution profile indicates that the formulations A6, B6 & C6 were similar.

CONCLUSION

Grinding of ARP with hydrophilic carriers improved the dissolution rate to variable extents. This effect was not only due to particle size reduction, but also resulted from the ability of these carriers to prevent aggregation of the finely divided drug particles, to improve wettability and to inhibit recrystallization during dissolution. Ground mixture containing MGG proved to be superior in increasing the dissolution rate followed by GG and HPMC. Ground mixture has shown significantly higher specific surface area and solubility than solid dispersion and physical mixture

REFERENCES

1. Leuner .C, Dressman.J. Improving drug solubility for oral delivery using solid dispersions.Eur j Pharm.Biopharm.2000; 50:47-60.
2. Hancock. B.C, Park. M. Characteristic and significance of the amorphous state in pharmaceutical systems J Pharm Sci. 1997; 86:1 – 12.
3. Khouzagar. K, Clas. S.D. Crystallization inhibition in solid dispersions of MK – 0591 and poly (vinylpyrrolidine) polymers.J.Pharm Sci. 2000; 89: 1325 – 1334.
4. Richard, A.M. & Benigni, R. (2002). AI and SAR approaches for predicting chemical carcinogenicity: survey and status report. *SAR and QSAR in Environmental Research* 13, 1.19.
5. Taku Nagai1, Rina Murai, Kanae Matsui, Hiroyuki Kamei, Yukihiro Noda, Hiroshi Furukawa and Toshitaka Nabeshima. Improvement in Solubility of Poorly Water Soluble Drug by Co-grinding with Highly Branched Cyclic Dextrin, J InclPhenMacro Chem 2006; 56: 2006, 61-64.
6. Nikolakakis, I. Kachrimanis. K, Malamataris, S. Relations between crystallization conditions and micromeritic properties of ibuprofen. Int.J.Pharm.2000; 201:79 – 88.
7. Ambarish H. Vadher, Jolly R. Parikh, Rajesh H. Parikh and Ajay B. Solanki, Preparation and Characterization of Co-Grinded Mixtures of Aceclofenac and Neusilin US2 for Dissolution Enhancement of Aceclofenac , AAPS PharmSciTech2009;1:606-614.

8. Arpansiree Wongmekiat, Satoko Yoshimatsu, Yuichi Tozuka, Kunikazu Moribe and Keiji Yamamoto. Investigation of Drug Nanoparticle Formation by Co-grinding with Cyclodextrins: Studies for Indomethacin, Furosemide and Naproxen.J InclusPhenand Macrocyclic Chem2006; 56: 29-32.
9. Craig, D.Q.M. Thae mechanisms of drug release from solid dispersions in water soluble polymers. Int.J.Pharm.2002; 231:131 – 144.
10. Thoma K, Knott F, Retardation of weakly basic drugs.5. Optimization of availability with papavarine and codeine in diffusion pellets, Pharm. Ind 1989; 51; 540-543.
11. Jayaraman D, Subramanian C, Ramaswamy P. Evaluation of Gibb's free energy nucleus kinetics of YBCO. J MaterSci letters. 2007; 1095): 292 – 296.
12. Alazar N. Ghebrenerkel, Chandra Vemavarapu, Mayur Ladayar. Use of surfactants as plasticizer in preparing solid dispersion of poorly sloluble API.Stability testing of selected solid dispersions.2007; 23(8):1928 – 1936.
13. Paul J Goodnick, Jason M JerryAripiprazole: profile on efficacy and safety. 2002: 3:1773-1781.
14. Doris E Braun, Thomas Celbrich, Volker Kahlenberg, Richard Tessadri, Josef Wieser, Ulrich J Griesser.Conformational plymrphism in aripiprazole; Preparation, stability and structure of five modifications.J Pharm Sci. 2009; 98(6):2010- 2020.
15. Limor Tessler, Israel Goldberg. Crystal structures of aripiprazole. A new anti psychotic drug and its inclusion compounds with methanol, ethanol and water. J Incl Phenom Macrocyclic Chem. 2006;55: 255-261
16. Rubinstein M.H, MusihabammaP.A. Universal friability test of tablet granules. Pharmaz Acta Helv. 1978; 71:125 – 129.
17. .Korsemeyer R., Gurny R., Peppas N, Mechanisms of solute releasefrom porous hydrophilic polymers. Int J Pharm, 15, 1983, 25-35.
18. Wagner JG, Interpretation of percent dissolved-time plots derivedfrom in vitro testing of conventional tablets and capsules. J PharmSci., 58, 1969, 1253-1257.
19. Higuchi T, Rate of release of medicaments from ointment basescontaining drugs in suspension. J Pharm Sci., 50, 1961, 874-875.
20. Hixson AW, Crowell JH, Dependence of reaction velocity uponsurface and agitation. Ind Eng Chem., 23, 1931, 923-931.
21. Harland, RS, Gazzaniga, A, Sangalli, ME, Colombo P, Peppas, NA.Drug/polymer matrix swelling and dissolution. Pharm. Res., 5, 1988,488-494.22.
22. Baker RW, Tuttle, ME, Kelly DJ, and Lonsdale, HK. Coupled transportmembranes: I. Copper separations. J. Membrane Sci., 2, 1977,213-233.
23. Morissette S.L, Almarsson o, Peterson M.L, Remenar J.F, Read M.J, Lemmo A.V, Ellis S, Cima M.J, Gardner C.R. High throughput crystallization :polymorphs, salts, cocrystals and solvates of pharmaceutical solids.Adv Drug Del Rev 2004; 56:275 0- 300.
24. Gowda D.V, Rajesh N, Afrasin Moin, Shivakumar H.G. Siddaramaiah. Controlled release behaviour of nifedipine from the pellets of gellucire/ microcrystalline cellulose blends. Int. J. Pharm Tech. Res, 2010; 2: 1215-1226.
25. Ostuka M, Matsumoto T, Kaneniwa N. Effects of environmental temperature on polymorphic solid state transformation of indomethacin during grinding. Chem Pharm Bull. 1986; 34: 1784 – 17 93.
26. LI Jian-feng1, LIU Ai-xiang1, XIA Guang-xin1, NIAN Yi-feng2, SHEN Jing-shan1.Spectroscopic Studies of Aripiprazole.Spectr Spectral Anal 2007; 27:863 – 867.
27. Garekani H, Sadeghi F, Badiee A, Mustafa S, Rajabhishi hbhoomi A. Crystal modification of ibuprofen and theisr physico mechanical . Drug Dev Ind Pharm 2001: 27; 8093 – 809.
28. Ostuka M, Matsumoto T, Kaneniva N. Effect of environmental temperature on polymorphic solid state transformation of indomethacin durnig grinding. Chem Pharm Bull 1986: 34; 1784 – 1793.
29. Kyeo-Re Lee, Eun-Jung Kim, Sang-Wan Seo and Hoo-Kyun Choi. Effect of poloxamer on the dissolution of felodipine and preparation of controlled release matrix tablets containing felodipine. Arch Pharma Res 2008;31; 1023-1028
30. Kyeo-Re Lee, Eun-Jung Kim, Sang-Wan Seo and Hoo-Kyun Choi. Effect of poloxamer on the dissolution of felodipine and preparation of controlled release matrix tablets containing felodipine , Archives of Pharmacal Research 2008;11: 1023-1028.
31. Rajesh KS, Khanrah A, Biswanath SA. Release of ketoprofen from alginate microparticles containing film forming polymers. J. Sci. Ind. Res., 2003; 27: 965 – 989.
32. Conte U, Sangali M. La Manna A. Swelling activated drug delivery system. Biomater. 9: 489 - 493.