# Dissolution rate enhancement of piroxicam by ordered mixing

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**Abstract**: Micronized piroxicam was mixed with lactose, mannitol, sorbitol, maltitol and sodium chloride to produce ordered mixture in a glass vial by manual hand shaking method. The effect of excipients, surfactant, superdisintegrant, drug concentration and carrier particle size on dissolution rate was investigated. Dissolution rate studies of the prepared ordered mixtures revealed that all water soluble excipients increased the dissolution rate of piroxicam when compared to the dissolution rate of piroxicam or its suspension. Ordered mixture formulation PLF4, consisting of lactose as water soluble excipient, SSG (8% w/s) and SLS (1% w/w), released piroxcam at a very fast rate so much so that about 90% of the composition had passed into solution within 2 min. The order of the dissolution rate enhancement for ordered mixtures of various water soluble excipients was: lactose > mannitol > maltitol > sorbitol > sodium chloride. Carrier granules of size 355-710 µm were most effective in increasing the dissolution rate of drug from ordered mixtures. Decreasing the carrier particle size reduced drug dissolution from ordered mixtures. The dissolution rate of ordered mixtures consisisting of 1-5% w/w piroxicam was superior to dissolution rate of piroxicam suspension. The dissolution data fitting and the resulting regression parameters indicated Hixson Crowell, cube root law, as the best fit to drug release data of ordered mixtures.

**Keywords**: Piroxicam, BCS class II drug, excipient, dissolution, ordered mixture.

## INTRODUCTION

Piroxicam is a cyclo-oxygenase inhibiting, non-steroidal anti-inflammatory agent (NSAID) that is used in treatment of rheumatoid arthritis, osteoarthritis, musculoskeletal disorders, dysmenorrhea, and postoperative pain (Pubchem, 2009). Piroxicam is also indicated for ankylosing spondylitis, postoperative pain, acute gout, dentistry, and episiotomy (Roberts and Morrow, 2001; Tripathi, 2004). Intrinsic solubility (log $S_o$) expressed as the average log molar concentration ±1 standard deviation (S.D.) is 4.03±0.01 (Wassvik *et al*., 2006). It is having cLogP 1.89 cm/s and pKa 4.5:3.6 (Wassvik *et al*., 2006). Intrinsic dissolution rate at pH 1.2, 4.5 and 6.8 was determined as 0.022 ± 0.001 0.0043 ± 0.0006 0.088 ± 0.002 mg/min/cm$^2$ (Yu *et al*., 2004). According to the BCS (Biopharmaceutics Classification System) (Amidon *et al*., 1995),. piroxicam is regarded as class II drug characterized by a low water solubility and dissolution rate.

Several techniques have been used to improve the oral bioavailability of piroxicam by accelerating its dissolution rate. These include, mainly, reduction of the drug particle size (Swanepoel *et al*., 2000), increasing wettability by addition of hydrophilic fillers and surfactants (Swanepoel *et al*., 2000), preparing solid dispersions (Ingkatawornwong *et al*., 2001; Karatas *et al*., 2005; Pan *et al*., 2000; Pignatello *et al*., 2002; Tantishaiyakul *et al*., 1999; Valizadeh *et al*., 2007; Verma *et al*., 2003; Wu *et al*., 2008; Yuksel *et al*., 2003), and cyclodextrin (CD) inclusion complexation (Cavallari *et al*., 2002; Woodcock *et al*., 1993).

Ordered mixtures consist of adhered fine particles of a hydrophobic drug to the surfaces of larger particles of a water soluble carrier substance (Saharan *et al*., 2008). Literature revealed that lactose (Ibrahim *et al.*, 1989; Iida *et al.*, 2004; Nilsson *et al.*, 1988; Padmadisastra *et al.*, 1994; Swaminathan & Kildsig, 2000; Thiel & Nguyen, 1984; Thiel *et al.*, 1983), mannitol (Nilsson *et al.*, 1988; Westerberg & Nyström, 1991; Westerberg & Nyström, 1993), sorbitol (Ibrahim *et al.*, 1989; Nikolakakis & Newton, 1989; Nikolakakis *et al.*, 2002; Schmidth & Benke, 1985), and sodium chloride (de Villiers & van der Watt, 1989; de Villiers & Van der Watt, 1994; Ibrahim *et al.*, 1989; Mosharraf & Nystrom, 1999; Nystrom & Westerberg, 1986) were extensively used in preparation of ordered mixtures. The carrier particles dissolve in the presence of water, causing the adherent particles of pharmaceutical substance to disperse throughout the liquid. This eliminates the inherent tendency of the particles of hydrophobic drug to collect into not-readily dissolvable and dispersible aggregate.

Water soluble excipients (lactose, mannitol, maltitol, sorbitol and sodium chloride), superdisintegrant (sodium starch glycolate, SSG) and surfactant (sodium lauryl sulphate, SLS) were used for improving the dissolution rate of drugs in different formulae prepared by ordered mixing. The study was novel in aspect that the drug and excipients used for preparation of ordered mixtures have

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not been studied and reported so far. Furthermore, the study provides additional avenues for proper selection of excipients, especially water soluble excipients for preparation of tablets which dissolves the active ingredients quickly. Prepared ordered mixtures of adequate dissolution properties may be selected for direct compression of tablets by adding suitable diluents, lubricants and other additives.

## MATERIALS AND METHODS

### *Materials*

Piroxicam was a gift sample from Cipla (Manufacturing and Research Division, LBS marg, Vikhroli, Mumbai, India). Lactose (Lactochem Fine Powder; Domo Holland), mannitol (Pearlitol 200 SD; Roquette, Hetero Drugs), maltitol (Maltisorb P90; Roquette, Rhodia Chemicals), sorbitol (Neosorb P60; Roquette, Rhodia India), SSG (Glycolys LV; Roquette) were received as *ex-gratis* samples from Signet Chemical Corporation, Mumbai, India. Sodium chloride and SLS were procured from Central Drug House, New Delhi, India.

### *Methods*

#### Average particle size and size distribution of drug

Particle size and size distribution of piroxicam was determined by laser light diffraction. The equipment consisted of a Malvern Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK) including a Scirocco 2000 module for dry measurement purposes operating at 3.0 bar air pressure for dispersion. Evaluation of data was performed by Malvern software version 5.22 using the Fraunhofer approximation. It had been established that a sufficient dispersion of particles but no milling occurred at 3.0 bar air pressure. Polystyrene latex particles were used as dispersion medium.

#### Preparation of composite carrier granules

Water soluble excipient (mannitol or maltitol or lactose or sorbitol or sodium chloride), and/or SSG and/or SLS were mixed in V blender (200 g working capacity, customized V blender, Shakti Engineering, Ahmedabad, India) for 30 minutes. Absolute ethanol was added to the powder mixture to prepare dough. The dough was screened through sieve no. 16 (aperture size 1000 μm) and dried to obtain composite carrier granules.

#### Mixing of composite carrier granules and piroxicam

Ordered mixture of piroxicam (table 1) were prepared by placing the micronized drug between two layers of composite carrier granules in a borosil glass vial (10 ml) and shaken vigorously by hand for 5 min. This method was found to produce consistently good quality ordered mixtures when observed by photomicrographs and also content uniformity assessed by homogeneity studies. The procedure had advantage that it did not cause size reduction of carrier during mixing.

#### Sampling from ordered mixtures

Prepared ordered mixtures in the glass vial were spread on a piece of butter paper and six samples from different locations were collected with the help of stainless steel spatula.

#### Homogeneity of piroxicam in ordered mixtures

Accurately weighed ordered mixture (200 mg) was transferred to a volumetric flask (10 ml). Volume- was made up to the mark by methanol and sonicated (Ultrasonicator 6.5L200H, PCI Analytics, Mumbai, India) for 30 minutes. The liquid samples were then centrifuged. Supernatant aliquot (500 μl) was diluted with distilled water upto 10 ml and analyzed for absorbance at 353.5 nm $\lambda_{max}$. The concentration was read off from the standard calibration curve of piroxicam.

#### Particle size classification of ordered mixtures

British standard sieves (BSS) of mesh number 22, 44, 60, 85, 100 and 120 having aperture size 710 μm, 355 μm, 250 μm, 180 μm, 150 μm and 125 μm respectively were used for classification of ordered mixtures or powders. Sieves were arranged in order of their decreasing aperture size i.e. having a coarsest sieve at the top and finest at the bottom. A cover was placed on top and a pan was fitted below the finest sieve. Ordered mixture/powder was placed in the top sieve. Sieve stack was mounted in a sieve shaker unit and agitated for 15 minutes. Sieve stack was removed form the sieve shaker and different fractions of ordered mixtures/powders were collected from different sieves.

#### Scanning Electron Microscopy (SEM) studies

Perfectly dried sample of powder or ordered mixture was mounted onto the stubs using double-sided adhesive tape. Mounted sample was coated with gold palladium alloy (150-200 Aº) using fine coat ion sputter (Jeol, fine coat ion sputter, JFC-1100, Jeol, Japan). The samples were subsequently analyzed under the SEM (JSM 6100, Joel, Japan) for external morphology.

#### Dissolution studies of ordered mixtures

The dissolution studies were performed in USP 24 Type II (Paddle type) apparatus (TDT-08L, Electrolab, Mumbai, India) at rotational speed of 100 rpm in distilled water. Samples of ordered mixture (200 mg) were added to the 900 ml of distilled water, maintained at 37ºC ± 0.5ºC. Aliquots of 5 ml as samples were withdrawn for analysis and an equal amount of fresh distilled water was replaced in the dissolution vessel. Obtained samples were analyzed for their absorbance at 353.5 nm and concentration was determined by standard curve of piroxicam. The univariate ANOVA was applied on the dissolution data at each time point by using DDSolver (Zhang *et al.*, 2010) to determine significant time×group interaction between formulations.

**Table 1**: Piroxicam ordered mixture formulations

| Formulation Code | Water Soluble Excipient | Superdisintegrant (8% w/w) | Surfactant (1% w/w) | Powder Fraction (μm) | Drug Conc. (% w/w) |
|---|---|---|---|---|---|
| PLF1 | Lactose | ----- | ----- | 125-710 | 5 |
| PLF2 | Lactose | SSG | ----- | 125-710 | 5 |
| PLF3 | Lactose | ----- | SLS | 125-710 | 5 |
| PLF4 | Lactose | SSG | SLS | 125-710 | 5 |
| PLF5 | Lactose | SSG | SLS | 355-710 | 5 |
| PLF6 | Lactose | SSG | SLS | 250-355 | 5 |
| PLF7 | Lactose | SSG | SLS | 180-250 | 5 |
| PLF8 | Lactose | SSG | SLS | 150-180 | 5 |
| PLF9 | Lactose | SSG | SLS | 125-710 | 1 |
| PLF10 | Lactose | SSG | SLS | 125-710 | 7 |
| PLF11 | Lactose | SSG | SLS | 125-710 | 10 |
| PMF1 | Mannitol | ----- | ----- | 125-710 | 5 |
| PMF2 | Mannitol | SSG | ----- | 125-710 | 5 |
| PMF3 | Mannitol | ----- | SLS | 125-710 | 5 |
| PMF4 | Mannitol | SSG | SLS | 125-710 | 5 |
| PMF5 | Mannitol | SSG | SLS | 355-710 | 5 |
| PMF6 | Mannitol | SSG | SLS | 250-355 | 5 |
| PMF7 | Mannitol | SSG | SLS | 180-250 | 5 |
| PMF8 | Mannitol | SSG | SLS | 150-180 | 5 |
| PMF9 | Mannitol | SSG | SLS | 125-710 | 1 |
| PMF10 | Mannitol | SSG | SLS | 125-710 | 7 |
| PMF11 | Mannitol | SSG | SLS | 125-710 | 10 |
| PSF1 | Sorbitol | ----- | ----- | 125-710 | 5 |
| PSF2 | Sorbitol | SSG | ----- | 125-710 | 5 |
| PSF3 | Sorbitol | ----- | SLS | 125-710 | 5 |
| PSF4 | Sorbitol | SSG | SLS | 125-710 | 5 |
| PSF5 | Sorbitol | SSG | SLS | 355-710 | 5 |
| PSF6 | Sorbitol | SSG | SLS | 250-355 | 5 |
| PSF7 | Sorbitol | SSG | SLS | 180-250 | 5 |
| PSF8 | Sorbitol | SSG | SLS | 150-180 | 5 |
| PSF9 | Sorbitol | SSG | SLS | 125-710 | 1 |
| PSF10 | Sorbitol | SSG | SLS | 125-710 | 7 |
| PSF11 | Sorbitol | SSG | SLS | 125-710 | 10 |
| PMTF1 | Maltitol | ----- | ----- | 125-710 | 5 |
| PMTF2 | Maltitol | SSG | ----- | 125-710 | 5 |
| PMTF3 | Maltitol | ----- | SLS | 125-710 | 5 |
| PMTF4 | Maltitol | SSG | SLS | 125-710 | 5 |
| PMTF5 | Maltitol | SSG | SLS | 355-710 | 5 |
| PMTF6 | Maltitol | SSG | SLS | 250-355 | 5 |
| PMTF7 | Maltitol | SSG | SLS | 180-250 | 5 |
| PMTF8 | Maltitol | SSG | SLS | 150-180 | 5 |
| PMTF9 | Maltitol | SSG | SLS | 125-710 | 1 |
| PMTF10 | Maltitol | SSG | SLS | 125-710 | 7 |
| PMTF11 | Maltitol | SSG | SLS | 125-710 | 10 |
| PSCF1 | Sodium Chloride | ----- | ----- | 125-710 | 5 |
| PSCF2 | Sodium Chloride | SSG | ----- | 125-710 | 5 |
| PSCF3 | Sodium Chloride | ----- | SLS | 125-710 | 5 |
| PSCF4 | Sodium Chloride | SSG | SLS | 125-710 | 5 |
| PSCF5 | Sodium Chloride | SSG | SLS | 355-710 | 5 |
| PSCF6 | Sodium Chloride | SSG | SLS | 250-355 | 5 |
| PSCF7 | Sodium Chloride | SSG | SLS | 180-250 | 5 |
| PSCF8 | Sodium Chloride | SSG | SLS | 150-180 | 5 |
| PSCF9 | Sodium Chloride | SSG | SLS | 125-710 | 1 |
| PSCF10 | Sodium Chloride | SSG | SLS | 125-710 | 7 |
| PSCF11 | Sodium Chloride | SSG | SLS | 125-710 | 10 |

SLS: sodium lauryl sulphate; SSG: sodium starch glycolate; NaCl: sodium chloride, Powder fractions: #22/120 = 125-710 μm; #22/44 = 355-710 μm; #44/60 = 250-355 μm; #60/85 = 180-250 μm; #85/100 = 150-180 μm

**Dissolution studies of pure piroxicam and its suspension**

The pure drug (aggregate form) and suspension of the drug equivalent to the amount contained in ordered mixtures were also analyzed for dissolution rate. Drug suspension was prepared in distilled water and added 0.5% SLS and stirred for 5 min. by propeller mixer. All the dissolution studies were performed in triplicates and their average results have been reported.

**Mathematical modeling of release kinetics**

In vitro drug release data were fitted to various release kinetic models (Ahuja *et al.*, 2007; Costa & Lobo, 2001), *viz.*, zero order, first-order, Higuchi and Hixson-Crowell cube roo employing the following set of equations:

First-order model

$\ln(M_t/M_o) = k_1 t$

Zero-order kinetic model

$Mo - Mt = k_o t$

Higuchi model

$M_t = K\sqrt{t}$

Hixon-Crowell cube root model

$(W_o)^{1/3} - (W_t)^{1/3} = k_{1/3} t$

where, $M_o$, $M_t$ and $M_\infty$ correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. The terms $W_o$ and $W_t$ refer to the weight of the drug taken initially and at time t, respectively. Various other terms *viz.* $k_o$, $k_1$, $k_{1/3}$ and K refer to the release kinetic constants obtained from the linear curves of zero-order, first-order, Hixson-Crowell cube root law and Higuchi model, respectively.

## RESULTS

***Drug particle size, homogeneity of ordered mixtures and scanning electron micrographs***

Micronized piroxicam was used for preparation of various ordered mixtures. The surface weighted mean diameter and volume weighted mean diameter of drug particles were 2.901 µm and 3.396 µm respectively. Specific surface area of piroxicam drug particles was 1.97 $m^2/g$. Particle sizes for 0.1%, 50% and 90% volume under size were 1.894 µm, 3.180 µm and 5.217 µm respectively.

Manual hand shaking method was found consistent to produce good quality ordered mixtures, RSD (%) for

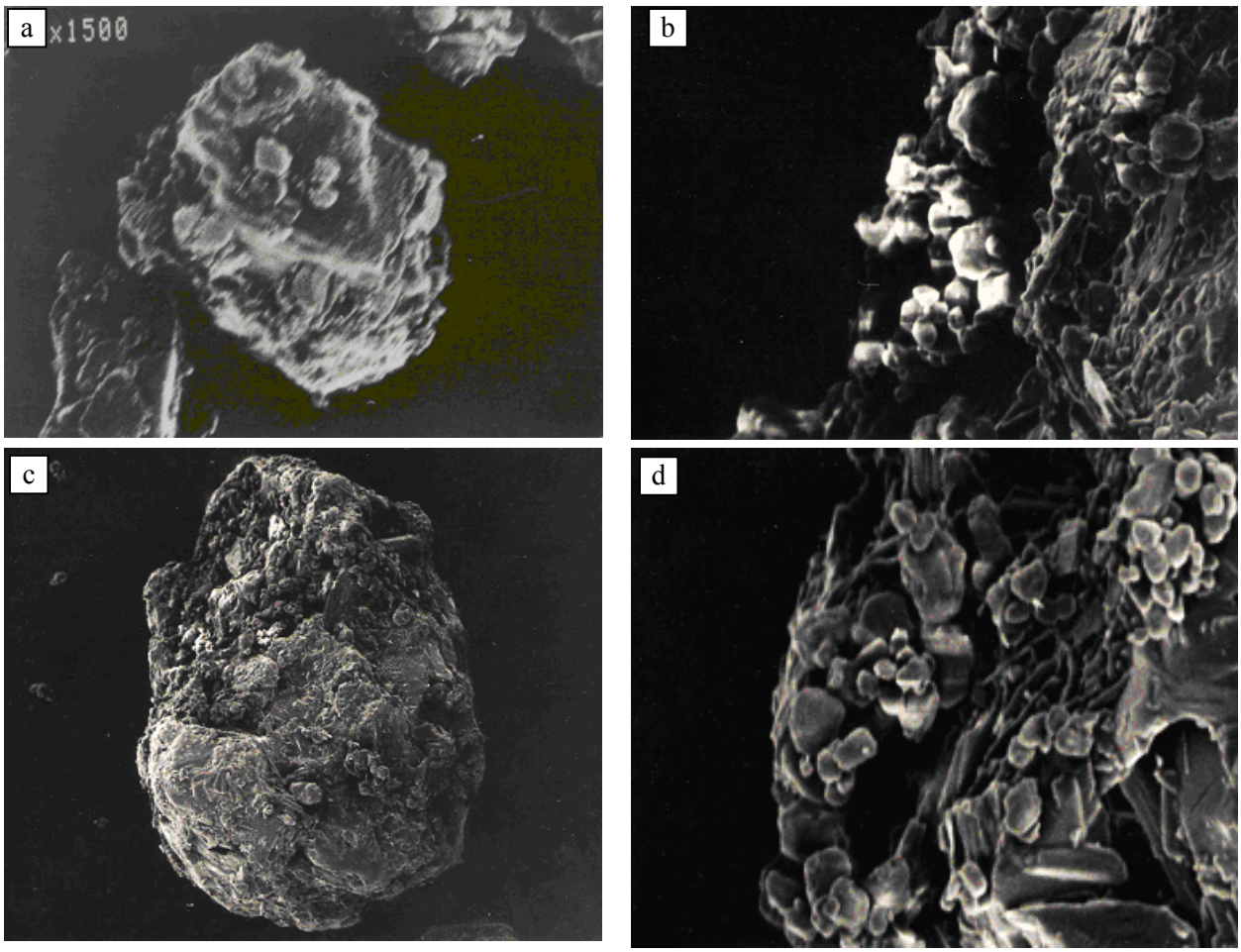


**Fig. 1**: Photomicrograph of ordered mixtures of piroxicam with different granules (a) lactose granules (×1500) (b) lactose granules surface view (×2100) (c) mannitol granule (×1500) (d) mannitol granule surface view (×2500).

different formulations were less than 2.5 (table 2). The procedure had the advantage that it did not cause size reduction of carrier during mixing. Furthermore, fewer amounts of drug and carrier were required.

**Table 2**: Homogeneity studies of piroxicam ordered mixtures.

| Formulation Code | Average Assay* (%) | SD | RSD (%) |
|---|---|---|---|
| PLF4 | 99.29 | 2.48 | 2.5 |
| PMF4 | 101.13 | 1.12 | 1.1 |
| PMTF4 | 101.39 | 2.17 | 2.14 |
| PSF4 | 101.78 | 1.11 | 1.09 |
| PSCF4 | 101.96 | 1.97 | 1.94 |

* Each value is an average of six determinations.

Scanning electron photomicrographs (fig. 1) of piroxicam ordered mixture with granules of lactose and mannitol were obtained. Granules of lactose and mannitoltol adsorbed with piroxicam particles were clearly visualized. The presence of crevices and surface irregularities in photomicrographs are considered potential sites where micronized piroxicam particles were lodged. More distinctive surface view of lactose granule (fig. 1b) and mannitol granule (fig. 1d) confirmed that micronized piroxicam particles were adhered to and distributed on the surface of large size carrier granules.

***Variables affecting release of piroxicam from ordered mixtures***

Ordered mixtures of piroxicam were evaluated by dissolution studies to determine the effect of formulation variables, carrier particle size and drug concentration.

***Effect of formulation variables***

At initial time points, 2 min., 5 min. and 60 min., drug release from pure drug powder (aggregate) and drug suspension was 4.98%, 7.69% and 44.56% respectively. Well stirred aqueous suspension of piroxciam released 59.62%, 76.14% and 86.09% drug at 2 min., 10 min. and 60 min. respectively. All the ordered mixture formulations of piroxicam increased the dissolution of piroxicam. Ordered mixture formulation PLF4, consisting of lactose as water soluble excipient, SSG (8% w/s) and SLS (1% w/w), released piroxcam at a very fast rate so much so that about 90% of the composition had passed into solution within 2 min. The dissolution rate enhancement with different water soluble excipients was in the order: lactose > mannitol > maltitol > sorbitol >

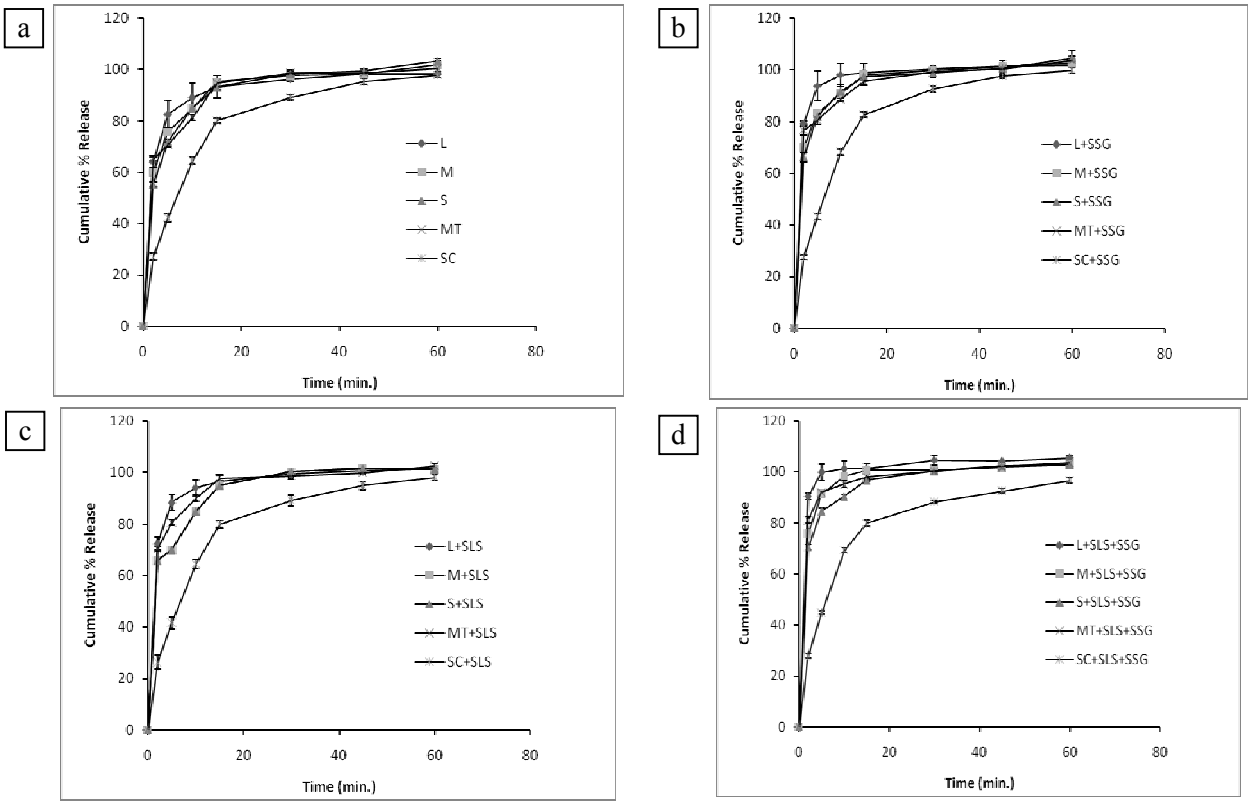


**Fig. 2**: Effect of different composition of carrier granules on dissolution rate enhancement of piroxicam from ordered mixtures. (a) Water soluble excipient without SSG and SLS (b) Water soluble excipient with SSG (c) Water soluble excipient with SLS (d) Water soluble excipient with SSG and SLS.

Abbreviations: L: Lactose; M: Mannitol; S: Sorbitol; MT: Maltitol; SC: Sodium Chloride; SSG: Sodium Starch Glycolate; SLS: Sodium Lauryl Sulphate

sodium chloride (fig. 2). The dissolution rate of ordered mixture formulations was superior to drug suspension except the formulations GSCF1-GSCF4 which had low dissolution rate at initial time points upto 10 min (fig. 3). However, the overall piroxicam dissolution rate of formulations GSCF1-GSCF4 improved after 10 min and was superior to dissolution rate of piroxicam from suspension (fig. 3e). The increase in dissolution rate by ordered mixing is attributed to an increase in the surface area available for dissolution by presenting the drug particles in the form of primary particles and the change in the hydrodynamic microenvironment around the particles.

The addition of superdisintegrant in granules (PLF2; PMF2; PSF2; PMTF2; PSCF2) contribute to increase in dissolution of piroxicam from ordered mixtures when compared to formulations lacking superdisintegrant (PLF1, PMF1, PSF1, PMTF1, PSCF1). Thus, the addition of superdisintegrant in all carriers increased dissolution of piroxicam from ordered mixtures (fig. 2b). The increase was maximum in PLF2 being 11.19% and 9.02% at 5 and 10 min. respectively when compared to PLF1 formulation. The minimum effect of superdisintegrant addition was observed in PSCF2 with only 3.71% at 10 minutes. Incorporation of superdisintegrant is supposed to be effective in causing the carrier particles to disintegrate

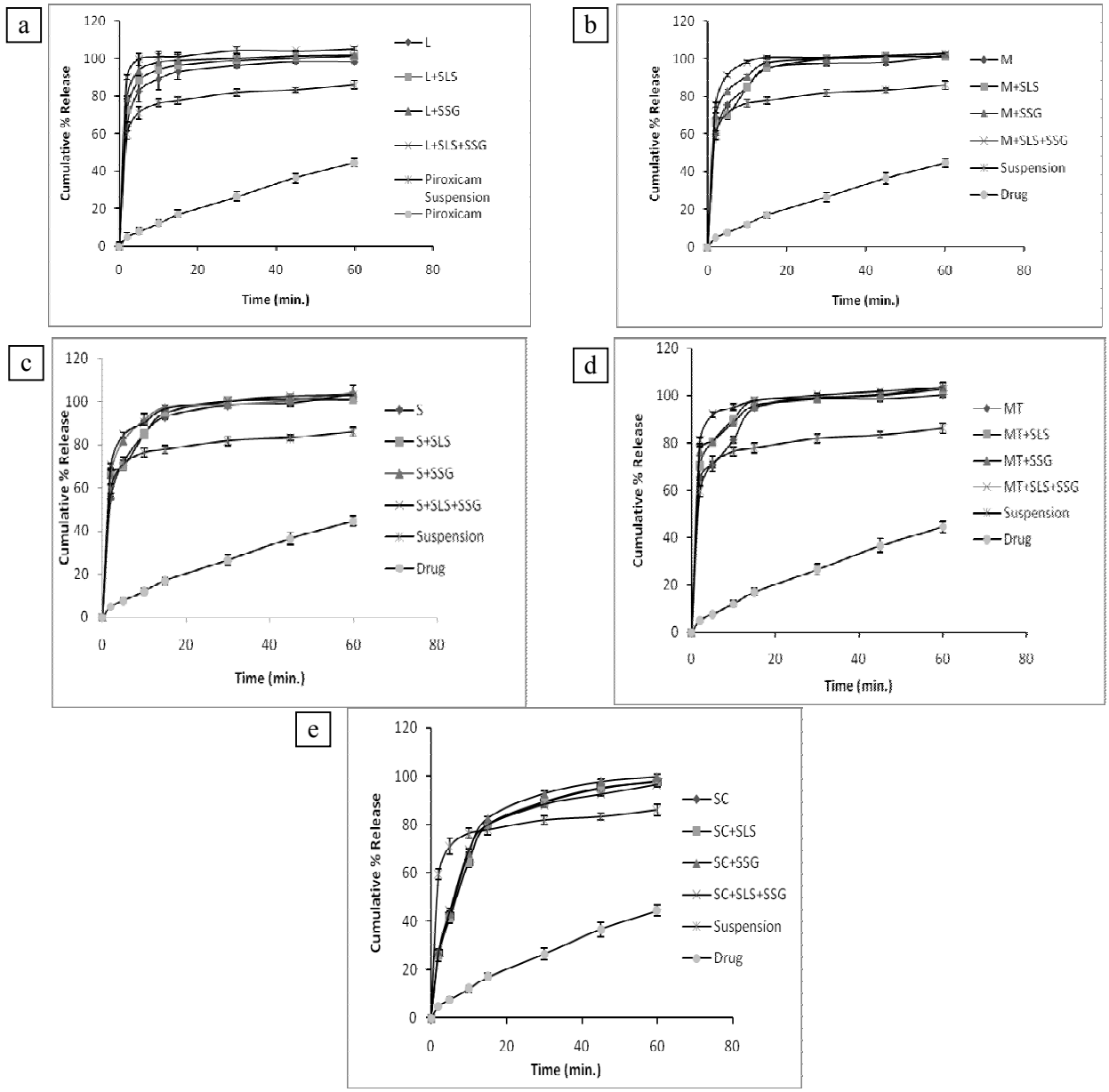


**Fig. 3**: Effect of formulation variables on drug release from ordered mixtures prepared from different water soluble excipients. (a) lactose (b) mannitol (c) maltitol (d) sorbitol (e) sodium chloride

Abbreviations: L: Lactose; M: Mannitol; S: Sorbitol; MT: Maltitol; SC: Sodium Chloride; SSG: Sodium Starch Glycolate; SLS: Sodium Lauryl Sulphate

and dissolve rapidly in contact with water, so as to release the individual, mutually discrete primary drug particles (Nystrom *et al*., 1989).

Incorporating surfactant in the ordered mixtures (PLF3, PMF3, PSF3, PMTF3, PSCF3) lead to an increase of 0-9%, at initial time points upto 10 min, in dissolution rate of piroxicam when compared to ordered mixture formulations which did not contain surfactant (PLF1, PMF1, PSF1, PMTF1, PSCF1 respectively) (fig. 3). When both superdisintegrant and surfactant were added (PLF4, PMF4, PSF4, PMTF4, PSCF4) to composite granule, synergistic effect of 5-14% increase on dissolution rate upto 10 minute was observed (fig. 3).

***Effect of carrier particle size***

Particle fraction 22/44 (355-710 µm) was found the most effective in improving the dissolution of piroxicam with all the carrier particles (fig. 4). Decreasing the particle size of carrier particles decreased the effect of dissolution enhancement with all the carrier particles. In sodium chloride ordered mixtures, the effect of particle size on dissolution rate was comparatively higher and more evident (fig. 4e). Fine ordered mixture (#85/100; 150-180

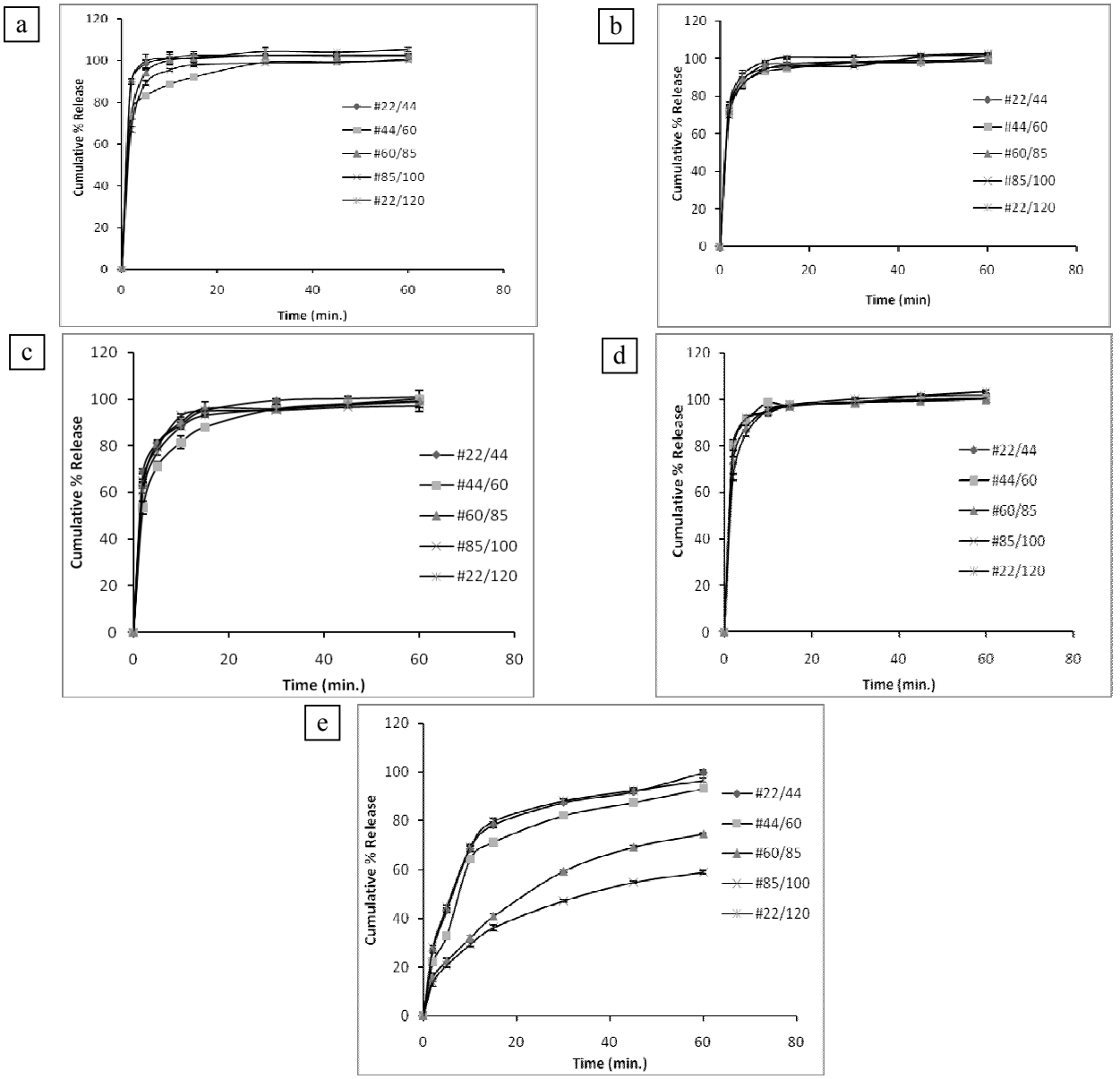


**Fig. 4**: Effect of carrier particle size on drug release from ordered mixtures prepared from different water soluble excipients. (a) lactose (b) mannitol (c) maltitol (d) sorbitol (e) sodium chloride

Notation of powder fraction: e.g., #22/44: Fraction of composite granule which passed through BSS sieve no. 22 and retained on BSS sieve no. 44. Powder fractions: #22/120 = 125-710 µm; #22/44 = 355-710 µm; #44/60 = 250-355 µm; #60/85 = 180-250 µm; #85/100 = 150-180 µm

μm; PSCF8) released about 36.16% drug while coarser ordered mixtures (#22/44, 355-710 μm; PSCF5) released 78.32% drug in 15 minutes, which signified a twofold increase. Coarser particles possess greater tendency to deviate from spherical size and possess cavities, capillaries and crevices which increases the chances of adhesion of the fine drug particles on the surface. The effect may affect the homogeneity of the formulation. Polydisperse carrier particles (#22/120; 125-710 μm; Formulations PLF4, PMF4, PSF4, PMTF4, PSCF4), mixture of all size ranges of particles, were equally effective to the coarsest size composite particles in improving the dissolution rate. This is presumably due to the effect of fines which are present along with the coarse carrier particles.

Fine particles of lactose (5% by weight) were added to ordered mixture and the effect on dissolution was observed. Piroxicam dissolution at initial time points was enhanced by 2% after such incorporation (fig. 5). Such effect was attributed to adsorption of fine particles on the surface of carrier particle and in between the micronized drug particles. This effect was supposed to additionally help in deagglomerating the drug particles. However it was also observed dissolution rate was superior when carrier particles of all size ranges were used (fig. 4). This may be due to the effect of fines which are present alongwith the coarse carrier particles.

***Effect of drug concentration***

Ordered mixtures of piroxicam and carriers were prepared at 1-10% w/w piroxicam concentration. Dissolution studies revealed that the dissolution was rapid in ordered mixture with 1-5% (fig. 6) drug concentration and superior to piroxicam suspension. However, when drug concentration was increased to 10%, the dissolution rate was either similar (figs. 6a to 6d) or inferior (fig. 6e) to piroxicam suspension. Comparative dissolution profiles of different ordered mixture revealed inverse relationship between drug concentration and dissolution rate (fig. 6). The drug concentration is, therefore, related to the coverage of carrier particles with drug particles which may be multimolecular when high drug concentrations were used.

***Mathematical modeling of the release kinetics***

The goodness of fit, for various models investigated for ordered mixtures, ranked in the order of Hixson-Crowell > Higuchi > First Order > Zero Order (table 3). The Hixson-Crowell model described drug release kinetics in the most befitting manner. The Higuchi model described the drug release data modestly with $R^2$ (regression coefficient) values ranging from 0.609 to 0.848. GMF4 and GSCF4 drug release data supported first order as well. Generally, the determination coefficients were low for all mathematical models except for Hixson-Crowell, therefore, the drug release kinetics for all the ordered mixture fitted best to the Hixson-Crowell model. The ordered mixtures disintegrate rapidly followed by quick dissolution of water soluble excipient (lactose, mannitol, sorbitol, maltitol and sodium chloride) thereby forming a drug suspension consisting of discrete primary drug particles. Wetting of hydrophobic drug particles is further aided by the presence of surfactant which also reduces aggregation. Surface specific dissolution rate increases as the particle size of hydrophobic drugs decreases, especially for micronized drugs. The dissolution rate enhancement is anticipated due to a rapid decrease in the thickness of the stagnant diffusion layer around micronized drug particles. Small diffusion boundary layer thickness results in faster transport of the dissolved molecules from the particle surface. Therefore, it is anticipated all the ordered mixture formulations followed the cube root law enunciated by Hixson Crowell.

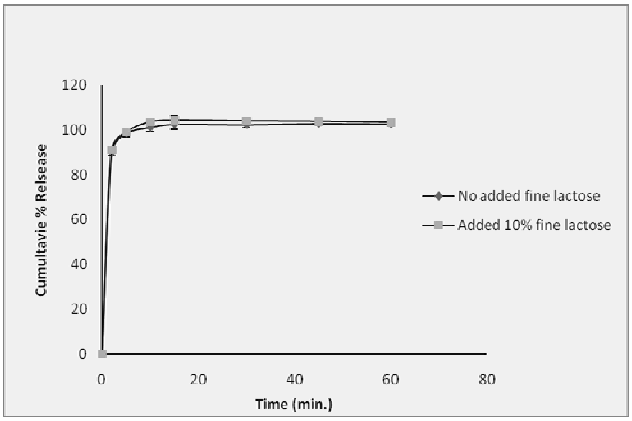


**Fig. 5**: Effect of carrier particle size on dissolution rate.

**Table 3**: Regression parameters of selected formulations obtained after fitting the drug release data to various release kinetics models.

| S. No. | Formu-lation | $R^2$ Values | | | |
|---|---|---|---|---|---|
| | | Zero Order | First Order | Higuchi | Hixson-Crowell |
| 1 | GLF4 | 0.547 | 0.586 | 0.691 | 0.696 |
| 2 | GMF4 | 0.449 | 0.915 | 0.609 | 0.983 |
| 3 | GSF4 | 0.652 | 0.588 | 0.87 | 0.971 |
| 4 | GMTF4 | 0.658 | 0.695 | 0.801 | 0.917 |
| 5 | GSCF4 | 0.702 | 0.937 | 0.848 | 0.99 |

***Comparison of dissolution data***

The dissolution parameters of ordered mixtures of piroxicam are enlisted in table 4. These ordered mixtures had different water soluble excipient, like lactose (PLF4), mannitol (PMF4), sorbitol (PSF4), maltitol (PMTF4) and sodium chloride (PSCF4), in the carrier granule composition. Ordered mixtures formulated with all water soluble excipients exhibited significant improvement in the dissolution parameters of the drug. Increase of 5.77 to

8.42 fold in cumulative percent drug release at 10 minute was observed. The order of dissolution rate enhancement was found was: lactose (PLF4) > maltitol (PMTF4) > mannitol (PMF4) > sorbitol (PSF4) > sodium chloride (PSCF4). The results indicated that PLF4 was superior formulation among all other ordered mixtures studied for dissolution rate enhacement. Relative dissolution rate (RDr) of different formulations indicated that at all sugar and sugar alcohols were equally effective in increasing dissolution rate upto 30 minute.

The results of univariate ANOVA (table 4) showed that the cumulative percents drug dissolved were significantly different at each time point for different formulations so time × group interactions were found to be significant in all formulations ($P<0.05$) when compared to piroxicam suspension, i.e. that percent drug dissolved are significantly different and the dissolution profiles are not parallel and all the prepared ordered mixture formulations and there is improvement in the dissolution rate. When the other ordered mixture formulations were compared to the PLF4 formulation ($P<0.05$) by univariate ANOVA, the percents drug dissolved from PMF4, PSF4, PMTF4 and PSCF4 were significantly different at all time points ($P<0.05$) which means that dissolution profiles were not parallel. The difference in drug dissolution rate was

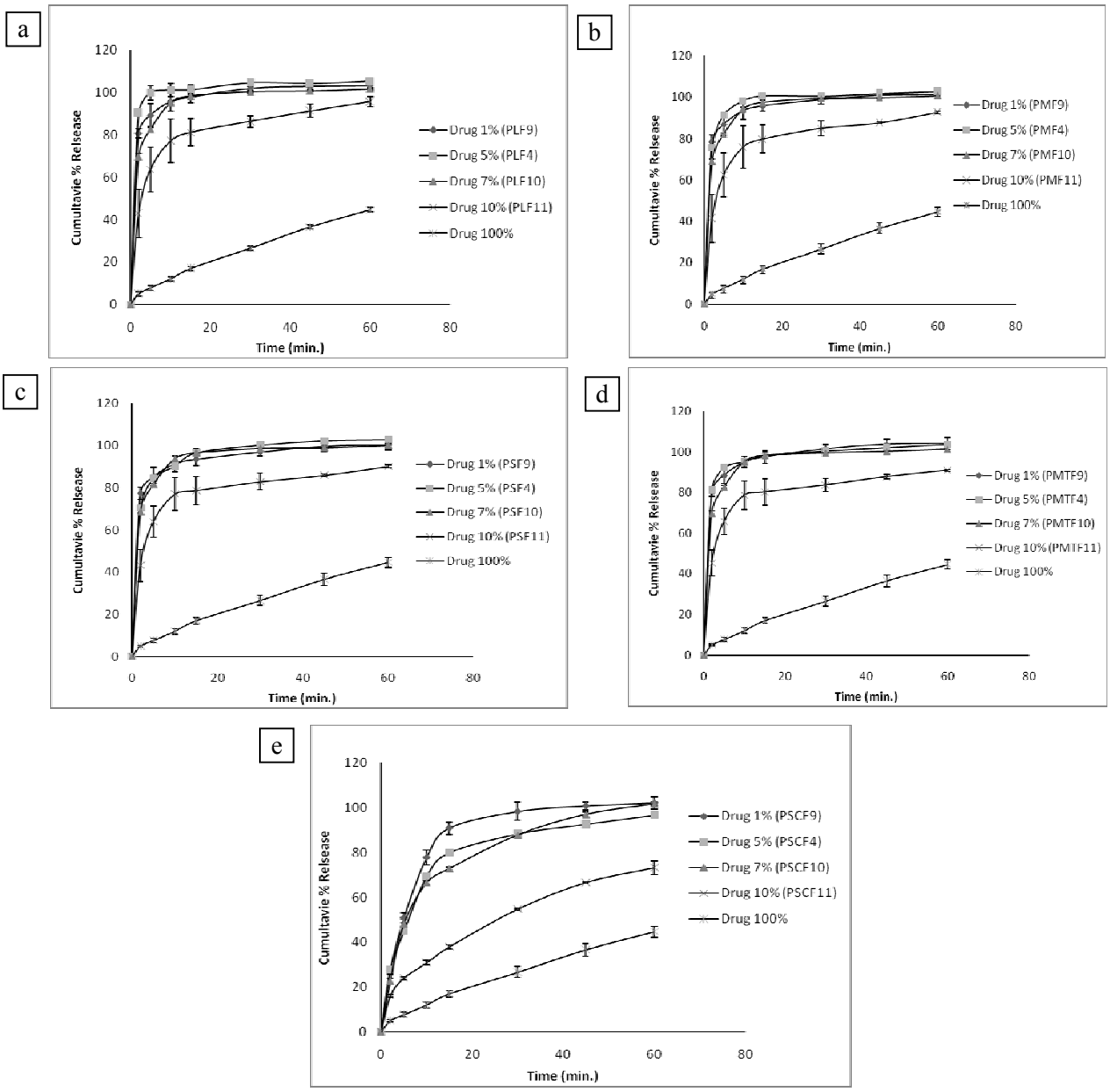


**Fig. 6**: Effect of drug concentration (% w/w) on drug release from ordered mixtures prepared from different water soluble excipients. (a) lactose (b) mannitol (c) maltitol (d) sorbitol (e) sodium chloride.

**Table 4**: Dissolution parameters of various ordered mixtures.

| S. No. | Formulation | Dissolution Parameters | | | | | |
|---|---|---|---|---|---|---|---|
| | | $DP^{a}_{2\ min}$ (%) | $DP^{a}_{10\ min}$ (%) | $DP^{a}_{60\ min}$ (%) | $DE^{b}_{5\ min}$ (%) | $DE^{b}_{15\ min}$ (%) | $RDr^{c}_{30\ min}$ |
| 1 | PLF4 | $90.26^{@}$ | $101.07^{@}$ | $105.36^{@}$ | 92.54 | 97.78 | 3.94 |
| 2 | PMF4 | $75.64^{\#@}$ | $98.33^{\#@}$ | $102.75^{\#@}$ | 83.57 | 98.62 | 3.79 |
| 3 | PSF4 | $70.4^{\#@}$ | $90.28^{\#@}$ | $102.88^{\#@}$ | 77.35 | 92.46 | 3.78 |
| 4 | PMTF4 | $81.13^{\#@}$ | $95.11^{\#@}$ | $103.52^{\#@}$ | 86.01 | 94.91 | 3.78 |
| 5 | PSCF4 | $27.83^{\#@}$ | $69.27^{\#@}$ | $96.61^{\#@}$ | 38.34 | 78.36 | 3.33 |
| 6 | Piroxicam Suspension | 59.62 | 76.43 | 86.09 | 31.17 | 36.77 | 3.09 |

[a] DP: Cumulative percent drug release at particular time.
[b] DE (%): Dissolution efficiency at particular time. Dissolution efficiency (%) up to 5 min ($DE_{5\ min}$) and 15 minutes ($DE_{15\ min}$) were calculated according to the following equation:

$$DE\% = \frac{\int_0^t y\,dt}{y_{100}\,t} \times 100$$

[c] $RDr_{30\ min}$: Relative dissolution rate at 30 minute, i.e., ratio of cumulative percent drug release from formulation at 30 minute to cumulative percent drug release from pure drug.
[#] Significant difference in cumulative percent drug release between the formulation and PLF4 formulation by univariate ANOVA, $p<0.05$, at the same time point.
[@]Significant difference in cumulative percent drug release between the formulation and piroxicam suspension by univariate ANOVA, $p<0.05$, at the same time point.

probably due to difference in solubilizing power of excipients, which needs to further explored.

## DISCUSSIONS

Carrier solubility is the most important factor in determining the degree of improvement in dissolution rate (Ibrahim *et al*., 1988). The dissolution rate of sparingly soluble, fine particulate, suspended drug is assumed to be diffusion-controlled (Bisrat *et al*., 1992). The apparent diffusional distance decreased substantially with particle size leading to an increase in dissolution rate. Thus, the apparent diffusional distance is relatively short for a free suspended drug particle and is a function of the particle size (Bisrat & Nystrom, 1988). When the same drug particle is released from the dissolving carriers it was suggested that the diffusional distance was even lower, resulting in a rapid dissolution rate (Westerberg & Nyström, 1993). Another study reported an ordered mixture of griseofulvin with various carriers, like sodium chloride, lactose, tricalciumdicitrate, emcompress (dicalciumphosphate dihydrate), glass beads and paraffins (Westerberg *et al*., 1986). The carriers possessing high solubility in the dissolution medium (sodium chloride, lactose and tricalciumdicitrate) showed high dissolution rates and the effect of agitation intensity was minimum. Micronized substances often form agglomerates, causing smaller surface area available to the solvents and resulting in a slower dissolution rate. Surfactants have been used to promote the dissolution of pharmaceutical substances in micronized form. Increased wettability and an increase in the apparent surface area play important roles in the marked improvement in drug dissolution (Ishizaka *et al*., 1993; Ishizaka *et al*., 1988). The increase in dissolution rate was thus attributed to deaggregation during the mixing process which produced a system in which the entire external surface of the drug particles was exposed to the dissolution medium. So, the system thus produced could be regarded as a well dispersed suspension of drug particles. Superdisintegrant swells at a rapid rate and thereby disintegrate the granule so that carrier particles dissolves at a faster rate which further increase the ability of the composite granule to release the individual, mutually discrete primary drug particles (Nystrom *et al*., 1989). Studies with griseofulvin and water soluble maltose/dextrose carrier indicated that the dissolution rates were inversely proportional to the concentration (McGinity *et al*., 1985). At higher concentrations, uneven coating of the drug was anticipated and it showed reduced dissolution rates particularly at loadings above monolayer coverage which resulted in incomplete drug deagglomeration.

In our studies, higher dissolution rate of piroxicam in ordered mixture is attributed to improved wetting of drug owing to attachment of smaller size drug particles on the surface of water soluble excipients, i.e., mannitol, lactose etc. Mannitol and lactose thus physically separates drug

particles thereby preventing aggregation in dissolution medium. Mannitol and lactose thus incite solubilizing effect by interacting with drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds but this phenomenon is drug and excipient-specific and need to be confirmed by further studies. The difference in ability of carrier particles to enhance dissolution rate is considered due to difference in the solubilizing effect in the dissolution medium. The hydrophilic carriers attract the dissolution medium and increase its amount in the immediate vicinity of the piroxicam surface. Addition of surfactant, SLS, to the ordered mixture further aids in reduction of surface tension of the dissolution medium thereby improved wetting and prevent aggregation of drug particles. Superdisintegrant, SSG, was helpful in disintegrating the granules and dispersing the discrete drug particles in the entire dissolution medium so that the system behaved like a well stirred aqueous dispersion.

## CONCLUSIONS

Micronized drugs can be formulated as ordered mixtures by simple, inexpensive manual mixing in a glass vial. Drug particles adsorb on the surface of water soluble carrier particles. Choice of carrier plays important role in dissolution enhancement. Lactose and mannitol were superior among all the water soluble excipients studied. Ordered mixture formulations quickly disperse the drug particles in the dissolution medium and thus provides a system which behaves similar to a well stirred aqueous suspension. Improvement in disintegration and wetting characteristics of ordered mixtures can be achieved by incorporation superdisintegrant and surfactant. High drug concentration, 10% w/w or more, on the carrier particles may retard the drug release by forming hydrophobic layers on water soluble carrier particles which may retard the quick dispersion of drug particles. Greater the size of carrier particles, higher will be the number of crevices and capillaries where the drug particles may adsorb. Hixson Crowell model described the drug release from ordered mixtures which is presumably due to surface specific drug dissolution from discrete piroxicam particles in distilled water.

## ACKNOWLEDGEMENT

The authors are thankful to the management of Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan for providing instruments and other laboratory facilities. Vikas A. Saharan wishes to acknowledge the administrative and motivational support of Prof. (Dr.) Vipin Kukkar, Director/Principal and Mr. Mahesh Kumar Kataria, Assistant Professor at Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan, India.

## REFERENCES

Ahuja N, Katare O and Singh B (2007). Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. *Eur. J. Pharm. Sci.,* **65**: 26-38.

Amidon G, Lennernas H, Shah V and Crison J (1995). A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and *in vivo* biovavailability. *Pharm. Res.,* **12**: 412-420

Bisrat M and Nystrom C (1988). Physicochemical aspects of drug release. VIII. The relation between particle size and surface specific dissolution rate in agitated suspensions. *Int. J. Pharm.,* **47**: 223-231.

Bisrat M, Anderberg EK, Barnett MJ and Nyström c (1992). Physicochemical aspects of drug release. XV. Investigation of diffusional transport in dissolution of suspended, sparingly soluble drugs. *Int. J. Pharm.,* **80**: 191-201.

Cavallari C, Albertini B, Gonzalez-Rodriguez ML and Rodriguez L (2002). Improved dissolution behaviour of steam-granulated piroxicam. *Eur. J. Pharm. Biopharm.,* **54**: 65-73.

Costa P and Lobo J (2001). Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.,* **13**: 123-133.

de Villiers MM and van der Watt JG (1989). Dissolution from ordered mixtures: The effect of stirring rate and particle characteristics on the dissolution rate. *Drug Dev. Ind. Pharm.,* **15**: 21-27.

de Villiers MM and Van der Watt JG (1994). The measurement of mixture homogeneity and dissolution to predict the degree of drug agglomerate breakdown achieved through powder mixing. *Pharm. Res,* **11**: 1557-1561.

Ibrahim H, Sallam EA, Takieddin M and Shamat MA (1988). Dissolution characteristics of interactive powder mixtures. Part One: Effect of solubility and particle size of excipients. *Drug Dev. Ind. Pharm.,* **14**: 1249-1276.

Ibrahim SA, Hafez E, El-Faham TH and Mohamed FA (1989). Dissolution enhancement of thiacetazone: II - via ordered mixing technique. *Powder Technol.,* **58**: 107-116.

Iida K, Inagaki y, Todo H, Okamoto H and Davnjo K (2004). Effects of surface processing of lactose carrier particles on dry powder inhalation properties of salbutamol surface. *Chem. Pharm. Bulll.,* **52**: 938-942.

Ingkatawornwong S, Kaewnopparat N and Tantishaiyakul V (2001). Studies on aging piroxicampolyvinyl-pyrrolidone solid dispersions. *Pharmazie,* **56**: 227-230.

Ishizaka T, Honda H and Koishi M (1993). Drug dissolution from indomethacin-starch hybrid powders prepared by the dry impact blending method. *J. Pharm. Pharmacol.,* **45**: 770-774.

Ishizaka T, Honda H, Ikawa K, Kizu N, Yano K and Koishi M (1988). Complexation of aspirin with potato

starch and improvement of dissolution rate by dry mixing. *Chem. Pharm. Bull.,* **36**: 2562-2569.

Karatas A, Yuksel N and Baykara T (2005). Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol. *Farmaco,* **60**: 777-782.

McGinity JW, Ku C-T, Bodmeier R and Harris MR (1985). Dissolution and uniformity properties of ordered mixes of micronized griseofulvin and a directly compressible excipient. *Drug Dev. Ind. Pharm.,* **11**: 891-900.

Mosharraf M and Nystrom C (1999). The effect of dry mixing on the apparent solubility of hydrophobic, sparingly soluble drugs. *Eur. J. Pharm. Sci.,* **9**: 145-156.

Nikolakakis I and Newton JM (1989). Solid state adspriton of antibiotics onto sorbitol. *J. Pharm. Pharmacol.,* **41**: 145-148.

Nikolakakis I, Newton JM and Malamataris S (2002). Solid state 'adsorption' of fine antibiotic powders onto sorbitol: effects of particle size, state of sorbed water and surface free energy characteristics. *Eur. J. Pharm. Sci.,* **17**: 229-238.

Nilsson P, Westerberg M and Nystrom C (1988). Physicochemical aspects of drug release. V. The importance of surface coverage and compaction on drug dissolution from ordered mixtures. *Int. J. Pharm.,* **45**: 111-121.

Nystrom C and Westerberg M (1986). The use of ordered mixtures for improving the dissolution rate of low solubility compounds. *J. Pharm. Pharmacol.,* **38**: 161-165.

Nystrom C, Westerberg M and Nilsson P (1989). A pharmaceutical composition. Patent WO 89/06533, 1989, Kabivitrum AB, Stockholm (SE).

Padmadisastra Y, Kennedy RA and Stewart PJ (1994). Influence of carrier moisture adsorption capacity on the degree of adhesion of interactive mixtures. *Int. J. Pharm.,* **104**: R1-R4.

Pan RN, Chen JH and Chen RR (2000). Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems. *Drug Dev. Ind. Pharm.,* **26**: 989-994.

Pignatello R, Ferro M and Puglisi G (2002). Preparation of solid dispersions of nonsteroidal anti-inflammatory drugs with acrylic polymers and studies on mechanisms of drug-polymer interactions. *AAPS PharmSciTech.,* **3**: E10.

Pubchem (2009). *http://pubchem.ncbi.nlm.nih.gov/*

Roberts LJ II and Morrow JD. (2001). Analgesic-antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout. In: (Eds) Hardman JG, Limbird LE and Gilman AG. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 10th ed.. McGraw-Hill, New York, pp.687-731.

Saharan V, Kukkar V, Kataria M, Kharb V and Choudhury P (2008). Ordered mixing: Mechanism, process and applications in pharmaceutical formulations. *Asian J. Pharm. Sci.,* **3**: 240-259.

Schmidth PC and Benke K (1985). 'Supersaturated' ordered mixtures on the basis of sorbitol. *Drugs Made Ger.,* **28**: 49-55.

Swaminathan V and Kildsig DO (2000). The effect of particle morphology on the physical stability of pharmaceutical powder mixtures: The effect of surface roughness of the carrier on the stability of ordered mixtures. *Drug Dev. Ind. Pharm.,* **26**: 365-373.

Swanepoel E, Liebenberg W, de Villiers MM and Dekker TG (2000). Dissolution properties of piroxicam powders and capsules as a function of particle size and the agglomeration of powders. *Drug Dev. Ind. Pharm.,* **26**: 1067-1076.

Tantishaiyakul V, Kaewnopparat N and Ingkatawornwong S (1999). Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. *Int. J. Pharm.,* **181**: 143-151.

Thiel WJ and Nguyen LT (1984). Fluidized bed film coating of an ordered powder mixture to produce microencapsulated order units. *J. Pharm. Pharmacol.,* **36**: 145-152.

Thiel WJ, Nguyen LT and Stephenson PL (1983). Fluidised bed granulation of an ordered powder mixture reduces the potential for ordered unit segregation. *Powder Technol.,* **34**: 75-80.

Tripathi KD (2004). Essentials of Medical Pharmacology. 6th Edn., Jaypee Brothers Medical. Publishers (P) Ltd, New Delhi, India, p.178.

Valizadeh H, Zakeri-Milani P, Barzegar-Jalali M, Mohammadi G, Danesh-Bahreini MA, Adibkia K and Nokhodchi A (2007). Preparation and characterization of solid dispersions of piroxicam with hydrophilic carriers. *Drug Dev. Ind. Pharm.,* **33**: 45-56.

Verma MM, Kumar MT, Balasubramaniam J and Pandit JK (2003). Dissolution, bioavailability and ulcerogenic studies on piroxicam-nicotinamide solid dispersion formulations. *Boll. Chim. Farm.,* **142**: 119-124.

Wassvik CM, Holmen AG, Bergstrom CA, Zamora I and Artursson P (2006). Contribution of solid-state properties to the aqueous solubility of drugs. *Eur. J. Pharm. Sci.,* **29**: 294-305.

Westerberg M and Nyström C (1991). Physicochemical aspects of drug release. XII. The effect of some carrier particle properties and lubricant admixture on drug dissolution from tableted ordered mixtures. *Int. J. Pharm.,* **69**: 129-141.

Westerberg M and Nyström C (1993). Physicochemical aspects of drug release XVII. The effect of drug surface area coverage to carrier materials on drug dissolution from ordered mixtures. *Int. J. Pharm.,* **90**: 1-17.

Westerberg M, Johnson MC and Nystrom C (1986). Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from ordered mixtures. *Int. J. Pharm.,* **28**: 23-31.

Woodcock BG, Acerbi D, Merz PG, Rietbrock S and Rietbrock N (1993). Supermolecular inclusion of piroxicam with beta-cyclodextrin: pharmacokinetic properties in man. *Eur. J. Rheumatol. Inflamm.,* **12**: 12-28.

Wu K, Li J, Wang W and Winstead DA (2008). Formation and characterization of solid dispersions of piroxicam and polyvinylpyrrolidone using spray drying and precipitation with compressed antisolvent. *J. Pharm. Sci.,* **98**: 2422-2431.

Yu LX, Carlin AS, Amidon GL and Hussain AS (2004). Feasibility studies of utilizing disk intrinsic dissolution rate to classify drugs. *Int. J. Pharm.,* **270**: 221-227.

Yuksel N, Karatas A, Ozkan Y, Savaser A, Ozkan SA and Baykara T (2003). Enhanced bioavailability of piroxicam using Gelucire 44/14 and labrasol: *In vitro* and *in vivo* evaluation. *Eur. J. Pharm. Biopharm.,* **56**: 453-459.

Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C and Xie S (2010). DDSolver: An add-in program for modeling and comparison of drug dissolution profiles. *In: The AAPS Journal*. Springer, New York, pp.263-271