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STUDY OF DISSOLUTION ENHANCEMENT PROPERTY OF POLOXAMER 407 USING BCS CLASS II DRUGS

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ABSTRACT

The aim of the current work was to examine the effect of micronized poloxamer 407 on the dissolution property of different poorly water-soluble drugs considered as BCS class II type. Micronized poloxamer 407 (Lµtrol® micro 127, BASF) is a hydrophilic block copolymer usually used in pharmaceutical preparations as solubilizing agent. Eight BCS class-II drugs namely atorvastatin, carbamazepine, carvedilol, etoricoxib, furosemide, glipizide, ibuprofen and spironolactone were used for this purpose. Physical mixing technique was followed to prepare the drug-poloxamer 407 mixture of 1:1 ratio. The mixture was pulverized with the help of a mortar-pestle. UV spectrophotometric analysis was used to investigate the presence of drug-polymer interaction if any. In vitro release study was carried out in a USP type II dissolution apparatus where the dissolution conditions were maintained according to USP technical data. There was no interaction found due to physical mixing. In case of all drugs, remarkable enhancement in the release was found. Particularly, poloxamer 407 was found very effective in increasing the dissolution property of carvedilol, glipizide, atorvastatin and furosemide. More importantly, almost 4-8 fold increase in the release was observed within first 5 minutes of dissolution compared with pure drug powder.

Key words: Physical mixing, Poloxamer 407, Dissolution enhancement, Hydrophilic polymer.

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INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs [1,2]. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration [3,4]. In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration [4, 5], which can detract from the drug's inherent efficacy [6–8]. Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window [9, 10] .Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability [9, 11]. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [6, 12, 13].

In drug discovery, about 40% of new drug candidates display low solubility in water, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity [17]. Therefore, producing suitable formulations is very important to improve the solubility and bioavailability of such drugs [18].

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [14–16].

Two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. To enhance dissolution hydrophilic polymers

are frequently used to prepare solid dispersions and self emulsifying drug delivery systems (SEDDS). But these formulations are normally associated with some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. Irreversible drugs/ excipients precipitation may also be problematic [4]. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation in SEDDS [19].

Physical mixing of practically insoluble drugs with hydrophilic polymers was confirmed as a valid approach to the improvement of dissolution, even in presence of other components. The reason for the poor dissolution of pure drug could be poor wettability and/or agglomeration or particles size. It was found that the dissolution rate of the drug increased according to increasing amount of hydrophilic carriers in physical mixture batches. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particles [20] [21].

Polyvinylpyrrolidone (PVP), polyethyleneglycol (PEG) and poloxamer are the hydrophilic polymers frequently used as carriers in SD and SEDDS. In this study the micronized form of poloxamer 407 was used only to physically mix it with different drugs. The intimate mixing of drug and poloxamer considerably increase dissolution of the drug.

EXPERIMENTALS
Materials

All the drugs and chemicals used in this research were of standard pharmaceutical grade. Nine poorly water soluble drugs were used for this study. The drugs were atorvastatin, carbamazepine, carvedilol, etoricoxib, fenofibrate, furosemide, glipizide, ibuprofen and spironolactone. All these drugs were gift samples from Incepta Pharmaceutical (BD) Limited. Micronized poloxamer 407 (Lµtrol® micro 127) was a generous gift from BASF, Germany.

Preparation of Drug-Poloxamer Physical Mixture

Physical mixing was done in a very simple way. Fixed amount of drug and poloxamer at 1:1 ratio

[Table-1] were mixed with the help of mortar-pestle. The drug-carrier mixtures were then filled in

screw-cap test tube and kept in desiccator to avoid any moisture exposure until further use.

Table 1. Physical mixtures of different drugs with poloxamer 407 and their λ_{max}

Drug	Amount of Drug	Micronized poloxamer	λ_{max} (nm)	
			Drug	Drug + poloxamer 407
Atorvastatin	10 mg	10 mg	241.4	241.3
Carbamazepine	15 mg	15 mg	284.6	284.8
Carvedilol	10 mg	10 mg	241	241
Etoricoxib	10 mg	10 mg	233.2	233.2
Fenofibrate	20 mg	20 mg	291.2	291
Furosemide	20 mg	20 mg	228.9	229
Glipizide	10 mg	10 mg	275.4	275.4
Ibuprofen	50 mg	50 mg	221.6	221.6
Spironolactone	15 mg	15 mg	242.6	242.6

Drug –Poloxamer Interaction Test

Briefly, drug was dissolved in methanol and then diluted to a definite concentration by the respective dissolution medium. Then the UV spectrum was obtained in a UV-Spectrophotometer (UV -1700 Pharma Spec**,** Shimadzu Corporation, Japan). Same procedure was performed for drug and poloxamer 407 mixture where the ratio of drug-poloxamer was 1:1. This experiment was performed to investigate any interaction present between the drug and poloxamer 407. The overlaid spectrum lines of the drug and drug- poloxamer mixture tells about the presence/absence of interaction as any shifting of lambda max (λ_{max}) value indicates the interaction of drug with polymer.

In vitro Dissolution Test

For the purpose of dissolution, USP Type-II dissolution tester (Veego, India) was used maintaining 75 rpm for all drugs. Dissolution media for different drugs were used according to the USP. At predetermined intervals of 5, 10, 15, 20, 30, 40, 50 and 60 minutes, samples were withdrawn,

filtered through a 0.45 µm filter paper (Whatman-1001055) and finally analyzed by a UV-VIS spectrophotometer (UV -1700 Pharma Spec**,** Shimadzu Corporation, Japan) at their respective λ_{max}.

RESULTS AND DISCUSSION:

Study of Drug-Poloxamer Interaction:

The lambda max (λ_{max}) values from different drugs and drug-poloxamer mixtures are given in Table 1. By observing the lambda max values, it is clear that very negligible changes occurred in the respective λ_{max} values of few of the drug while the drug-poloxamer physical mixtures were examined. Thus a conclusion can be made that there was no interaction between these drugs with poloxamer and there was no chance of misinterpretation of dissolution data obtained by different formulation of drugs with poloxamer.

In vitro Dissolution Study

The main purpose of this work was to evaluate the effect of poloxamer on the dissolution property of the drug. The percent release and dissolution rate

of different physical mixtures of the drugs are   described in Figure 1 and 2.

Figure 1. Release profile of 8 different BCS class II drugs from drug- poloxamer 407 physical mixture (1:1)
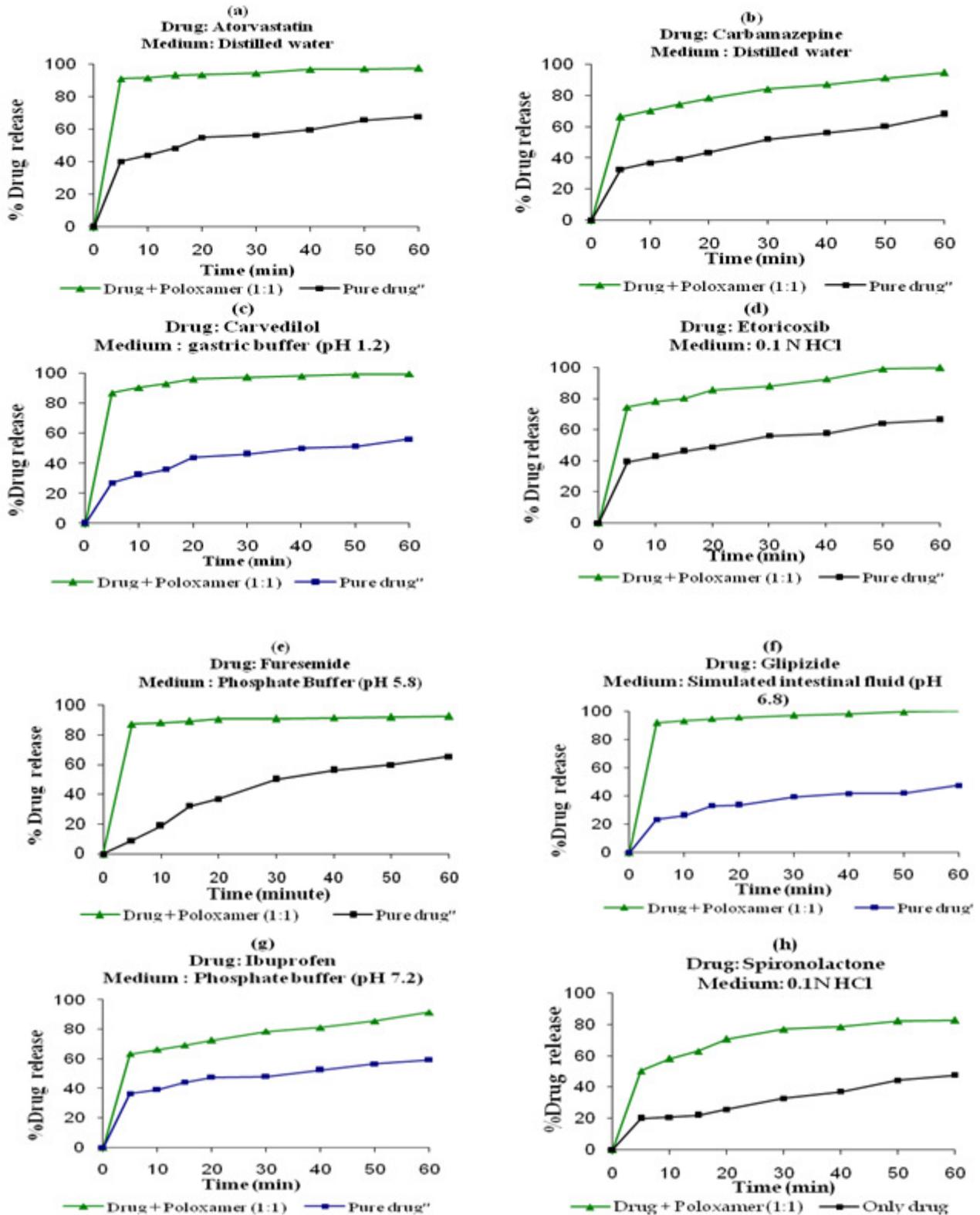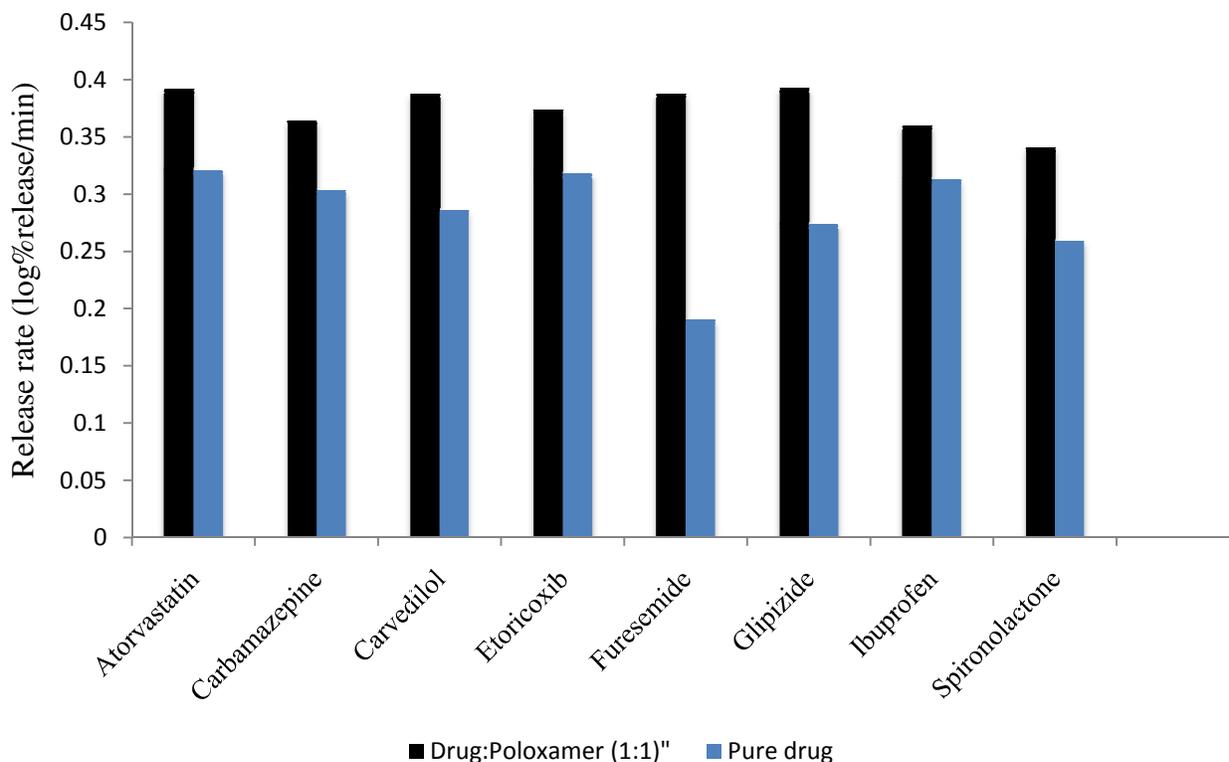
Figure 2. Comparative release rate of pure drug and drug- poloxamer 407 physical mixture (1:1).

Figure-1a shows 91% release of atorvastatin from physical mixture only after 5 minutes whereas the release of pure drug was only 40% after same time. The release was increased from this batch gradually up to 1 hour and completed its 100% release at 1 hour. Physical mixing of drug with a hydrophilic carrier results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media [22].

The dissolution rate of pure carbamazepine was poor and within first 5 minutes of dissolution, only 32.1%% drug was released [Figure-1b]. And after 60 minutes of dissolution, the release was only 65%. The reason for this poor dissolution of pure drug might be due to the poor wettability and/or agglomeration of particles. In contrast, drug release was found increased while it was mixed physically with poloxamer and it was 94.8% after 60 minutes of dissolution. This was due to the increase in solubility of drug by the presence of

hydrophilic carrier surrounding the drug particles [23].

Figure-1c shows that 86.9% carvedilol was released from physical mixture after 5 minutes of dissolution and the release reached 99.6% after 60 minutes. On the other hand, the release of drug from pure sample after 5 minutes and 60 minutes were 26.8% and 56.1% respectively. Marked rise in dissolution has been studied in different solid dispersions and self emulsifying drug delivery systems of carvedilol using hydrophilic polymers [24]. In this study kneading action provided significant dissolution improvement which is a proof of effective solubilization and wetting property of poloxamer 407. Similar observations have been reported for solid dispersions of naproxen in polyethylene glycols and nifedipine in Gelucire 50/13 with pluronic F68 [25].

Etoricoxib showed 39.1% release from pure drug after 5 minutes of dissolution [figure-1d]. Drug release was enhanced by two folds (74.8%) from physical mixture after same time. After 1 hour of

dissolution drug release from pure sample and physical mixture were 66.2% and 99.7% respectively. The crystalline nature of etoricoxib turns to amorphous when blended with fine kneading actions. The enhancement of dissolution in physical mixture is mainly attributed to increased surface area of drug exposed to large carrier molecules, increased wettability, and accordingly solubility due to polar effect of poloxamer [26]. This also may be attributed to the higher hydrophilic carriers, which can reduce the interfacial tension between the poorly aqueous soluble drugs and the dissolution medium [27].

Only 8.5% drug was released from pure furosemide within first 5 minutes of dissolution [figure-1e]. Within same time, 87.2% drug release was found from physical mixture which was more than 10 folds higher than the release from pure drug. As indicated by the dissolution data of the physical mixture, improvement of dissolution might be attributed to higher wettability and dispersibility of poloxamer [28].

Figure-1f shows 91.2% release of glipizide from physical mixture after 5 minutes of dissolution and after 60 minutes the release was 99.9%. This release was lot higher than the release from pure drug. Only 23.2% glipizide was released from pure drug within first 5 minute of dissolution. After 60 minutes, release from pure drug reached 47.1%. In physical mixture drug particles were in close contact with or adhere to polymer particles as a result of mixing. When this mixture came in contact with water, due to hydration the polymer particles turned into polymer solution, solubilizing the adjacent drug particles and subsequently releasing the drug into dissolution medium [29].

Figure-1g shows that the release of ibuprofen from physical mixture was 63.3% within 5 minute of dissolution while the release from pure sample was 36.2%. After 60 minutes, 92.6% drug was released from physical mixture. During dissolution, polymer solution was formed from polymer particles, resulting in increased wettability leading to enhanced local solubility of drug particles at the diffusion layer surrounding the particles. Finally the drug was released into the medium. This might also

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possibly explain the higher solubility of drug in phase solubility study where the ibuprofen particles were kneaded with hydrophilic polymers [30].

Spironolactone showed poor drug release (19.8%) from pure sample after 5 minutes of dissolution [Figure-1h]. At the same time drug release from physical mixture was 50.3% and after 60 minute it reached 83.1%. The enhanced release of drug from physical mixture compared to pure drug was due to particle size reduction and reduced agglomeration [31].

Release Rate of Drugs
The release rates of different drugs are depicted in figure 2. It is observed that release rates of drug from different physical mixtures were higher than that from pure drugs. The lack of release rate of different pure drugs was due to crystalline behavior of the drugs and also their tendency to agglomeration. The release profile of different pure drugs and their physical mixtures (with poloxamer) has been discussed in the section 3.2 of this article.

CONCLUSION
Among the eight model drugs, during the dissolution of atorvastatin, carvedilol, furosemide and glipizide, drug release from physical mixtures reached around 90% within only first 5 minutes. For the rest of the drugs the releases were significantly higher in case of physical mixture than pure drug. After 1 hour of dissolution drug release from all the physical mixtures reached between 95% and 100%. This dramatic improvement of dissolution of drug from physical mixture recognizes the unique contribution of poloxamer 407 in enhancing water solubility of poorly soluble drugs. As the physical mixing technique used in this study involves relatively simple preparation steps and poloxamer 407 was found as a highly effective solubility enhancer; a good combination of these two can be used for the preparation of granules, tablets, capsules and creams.

REFERENCES

1. Youn, Y.S. et al. (2006); Improved intestinal delivery of salmon calcitonin by Lys18- amine specific PEGylation: Stability, permeability, pharmacokinetic behavior and in vivo hypocalcemic efficacy. J. Contr. Release; 114: 334–342.

2. Sugawara, M. et al. (2005); The use of an in vitro dissolution and absorption system to evaluate oral absorption of two weak bases in pH-independent controlled-release formulations. Eur. J. Pharm. Sci. 26: 1–8.

3. Ikegami, K. et al. (2006); Bioavailability and in vivo release behavior of controlledrelease multiple-unit theophylline dosage forms in beagle dogs, cynomolgus monkeys, and go¨ttingen minipigs. J. Pharm. Sci.; 95: 1888–1895.

4. Charman, S.A. and Charman, W.N. (2003); Oral modified-release delivery systems. In Modified-Release Drug Delivery Technology (Rathbone, M.J. et al. eds), pp. 1–10, Marcel Dekker.

5. van Drooge, D.J. et al. (2006); Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int. J. Pharm.; 310: 220–229.

6. Vippagunta, S.R. et al. (2006); Factors affecting the formation of eutectic soliddispersions and their dissolution behavior. J. Pharm. Sci.; 96: 294–304.

7. Pouton, C.W. (2006); Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur. J. Pharm. Sci.; 29:278–287.

8. Bogdanova, S. et al. (2005); Interactions of poly(vinylpyrrolidone) with ibuprofen and naproxen: experimental and modeling studies. Pharm. Res. 22: 806–815.

9. Streubel, A. et al. (2006); Drug delivery to the upper small intestine window using gastroretentive technologies. Curr. Opin. Pharmacol. 6: 501–508.

10. Gardner, D. et al. (1997); The intelisite capsule: a new easy to use approach for assessing regional drug absortion from gastrointestinal tract; Pharm. Tech. Eur.; 9: 46–53.

11. Desai, J. et al. (2006); Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. Int. J. Pharm. 308: 115–123.

12. Tanaka, N. et al. (2006); Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): In vivo evaluation. J. Contr. Release 112: 51–56.

13. Ohara, T. et al. (2005); Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellulose and hydroxypropylmethylcellulose. Int. J. Pharm. 302, 95–102

14. Leuner, C. and Dressman, J. (2000;) Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm.; 50: 47–60.

15. Majerik, V. et al. (2007); Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. J. Supercrit. Fluids; 40: 101–110.

16. Prabhu, S. et al. (2005); Novel lipid-based formulations enhancing the in vitro dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam. Int. J. Pharm.; 301: 209–216.

17. Lipinski, C. (2002); Poor aqueous solubility—an industry wide problem in drug discovery. Am. Pharm. Rev. 5: 82–85.

18. Palmer, A.M. (2003); New horizons in drug metabolism, pharmacokinetics and drug discovery. Drug News Perspect. 16: 57–62.

19. Bo Tang, Gang Cheng, Jian-Chun Gu and Cai-Hong Xu (2008); Development of solid self

emulsifying drug delivery systems: preparation techniques and dosage forms; Drug discovery today; 13: 606-612.

20. Franca Ferrari, Moreno Bertoni, Cristina M. Bonferoni, Silvia Rossi, Carla Caramella and Gerard K. Bolhuis (1996); Dissolution Enhancement of an Insoluble Drug by Physical Mixture with a Superdisintegrant: Optimization with a Simplex Lattice Design; J. Pharm. Dev. Tech.; 2: 159-164.

21. Adrian C. Williams, Peter Timmins, Mingchu Lu, Robert T. Forbes; Disorder and dissolution enhancement: Deposition of ibuprofen on to insoluble polymers; Eur. J. Pharm. Sci.; 13: 288-294.

22. Leuner, C. and Dressman, J. (2000) Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50: 47–60.

23. ST Prajapati, MC Gohel and LD Patel (2007); Studies to enhance dissolution properties of carbamazepine; Ind. J. Pharm. Sci.; 67:427-430.

24. Gilles Dumortier, Jean Louis Grossiord, Florence Agnely and Jean Claude Chaumeil; A Review of Poloxamer 407 Pharmaceutical and Pharmacological Characteristics; Pharmaceutical Research; 23: 2709-2728.

25. Mura P, Manderioli A, Bramanti G, Ceccarelli L (1996); Properties of solid dispersions of naproxen in various polyethylene glycols. Drug Dev Ind Pharm.; 22: 909-916.

26. V. A. Saharan, V. Kukkar, M. Kataria, M. Gera, and P. K. Choudhury (2009); Dissolution enhancement of drugs part II: effect of carriers, Int. J. Health Research, 2: 207–223.

27. P. Mura, M. T. Faucci, and P. L. Parrini (2001); Effects of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties; Drug Dev. Indus. Pharm, 27: 119–128,.

28. Ganesh Chaulang, Piyush Patel, Sharwaree Hardikar, Mukul Kelkar, Ashok Bhosale and Sagar Bhise (2009); Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate; Trop. J. Pharm. Research; 8(1): 43-51.

29. D Chaudhary, S Kumar and G D Gupta; Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique; Asian J. Pharm; 14: 245-253.

30. Madhuri Newa, Krishna Hari Bhandari, Jong Oh Kim, Jong Seob Im, Jung Ae Kim, Bong Kyu Yoo, Jong Soo Woo, Han Gon Choi, and Chul Soon Yong (2008); Enhancement of Solubility, Dissolution and Bioavailability of Ibuprofen in Solid Dispersion Systems; Chem. Pharm. Bull. 56(4):569—574.

31. Duncan Q.M. Craig (2002); The mechanisms of drug release from solid dispersions in water-soluble polymers; Int. J. Pharm. 231: 131–144.

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