Effect of Additives on the Solubility and Dissolution of Piroxicam From Prepared Hard Gelatin Capsule

Eman B. H. Al-Khedairy*,[1]

*Department of Pharmaceutics , College of Pharmacy,University of Baghdad, Baghdad, raq.

Abstract

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of musculo-skeletal and joint disorders. The problem with this drug is its poor solubility in water and hence poor bioavailability after oral administration. In order to improve its solubility and dissolution behavior, hydrophilic additives such as starch, lactose, superdisintegrants including crospovidone (C.P), cross carmellose sodium (CCS), and sodium starch glycolate (SSG) were physically dry mixed with the drug by simple trituration. The improvement in the solubility in 0.1 N HCl was obtained as the amount of starch or lactose increased in the physical mixture, while for superdisintegrants, they further improve the solubility when they are present in small amount and the best improvement was gained with SSG. To study the effect of these additives on the dissolution of the drug, piroxicam capsules were prepared by simple trituration of the drug with starch or lactose or combination of lactose: starch (2:1)by weight with or with out the presence of SSG. The dissolution profiles of these preparations were analyzed using similarity factor f_2. Best results were obtained when the drug was triturated with starch and SSG or with acombinaton of lactose: starch (2:1) by weight with SSG . The dissolution profiles of these preparations were similar to that of the marketed Feldene ® Pfizer 20 mg capsules with f_2 74.6 and 80.37 respectively.

Key words: Piroxicam, hydrophilic additives, superdisintegrant

تأثير المواد المضافة على ذوبانية وتحرر دواء البيروكسيكام من الكبسولات الجيلاتينية الصلبة

ايمان بكر حازم الخضيري*،[1]

* فرع الصيدلانيات ، كلية الصيدلة ، جامعة بغداد، بغداد ، العراق.

الخلاصة

البيروكسكام هو من مضادات الالتهابات الغير ستيرويدية التي تستخدم في علاج آلام المفاصل والآلام العضلية . المشكلة مع هذا الدواء هي انه قليل الذوبان بالماء وبالتالي يكون التوفر الحيوي له ضئيلا عند تناوله كشكل دوائي عن طريق الفم . لذلك ولتحسين ذوبانه وتحرره من الشكل الدوائي تم اضافة مواد محبة للماء مثل النشاء ، اللاكتوز ، مواد مفككة قوية مثل (C.P) crospovidone ، cross carmellose sodium (CCS) و sodium starch glycolate (SSG) والتي تم مزجها مع الدواء بشكل جاف وبطريقة السحن الفيزياوي البسيط. تم الحصول على تحسن في الذوبانية في الوسط الحامضي (حامض الهيدروكلوريك ذو عيارية ٠.١) عند مزج الدواء مع النشا او اللاكتوز مع زيادة اي منهم في المزيج، اما بالنسبة للمواد المفككة القوية فقد وجد انها تحسن الذوبانية عند وجودها بكمية قليلة وان اكثرتحسن تم الحصول عليه باستعمال SSG . لغرض دراسة تأثير هذه المواد المضافة على سرعة تحرر الدواء من الشكل الدوائي ، تم تحضير كبسولات عن طريق مزج الدواء بطريقة السحن البسيط مع النشا او اللاكتوز او مزيج من اللاكتوز والنشا بنسبة وزنية (١:٢) بوجود او عدم وجود SSG . لقد تم تحليل نتائج تحررالدواء باستعمال معامل التشابه f_2 .احسن النتائج تم الحصول عليها عند سحن الدواء مع النشا و SSG او عند سحنه مع مزيج اللاكتوز والنشا بنسبة وزنية (١:٢) مع SSG حيث ان تحرر الدواء من هذه الكبسولات كان مشابه لتحرره من المنتج المسوق لكبسولات الفلدين ٢٠ ملغم لشركة فايزرحيث ان معامل التشابه f_2 كان ٧٤.٦ و ٨٠.٣٧ بالتعاقب.

الكلمات المفتاحية : البيروكسيسام ، مواد مضافة محبة للماء، مواد مفككة قوية .

Introduction

Sufficient solubility is a prerequisite for effective oral delivery of any therapeutic agent. However, drugs with low solubility and high permeability fall into Biopharmaceutics Classification System (BCS) class II [(1)] for which the dissolution is usually the rate-limiting step for gastrointestinal absorption. To enhance the dissolution rate and thus oral absorption of such drugs numerous formulation strategies have been developed [(2)]. Proxicam is a NSAID which is widely used for treatment of musculo-skeletal and joint disorders [(3)]. Its absolute bioavailability is unknown since no intravenous dosage data is available in man. It is practically insoluble in water [(3,4)]. Hence when this drug is administered orally it may cause bioavailability problems arises from its low water solubility and law dissolution rate in acid medium where the absorption takes place[(5)] .

[1] Corresponding author E- mail : emanalkhedairy@yahoo.com
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Various techniques have been used in an attempt to improve the solubility and dissolution rate of piroxicam including liquisolid compacts [6] , salt formation with ethanolamines [7], solid dispersion using PVP K30 [8] or PEG 4000 [9] as a water soluble carriers. In addition, surface solid dispersion of piroxicam in microcrystalline cellulose and in potato starch was also prepared by coevaporation method [10]. Moreover, it was found that the solubility and dissolution of poorly water soluble drugs can be markedly improved by the use of superdisintegrants using solid dispersion technique[11,12] or by preparation of ordered mixing or as physical mixture [11, 13]. The aim of this study was to determine the impact of simple physical mixing of piroxicam with different amount of starch, lactose, superdisintegrants including crospovidone, cross carmellose sodium, and sodium starch glycolate each alone on the solubility of drug in 0.1N HCl .In addition the effect of combination of piroxicam with one or more of the above additives on its dissolution from these physical mixtures enclosed in hard gelatin capsules was also explored and compared with that of pure drug and with the commercially available Feldene [R] 20 mg Pfizer capsules.

Materials and Methods

Materials

Piroxicam, sodium starch glycolate (SSG) (Samara Drug Industry (SDI), Iraq) crospovidone (C.P), cross carmellose sodium (CCS) (Dar Al-Dawa Pharmaceutical, Manufacturing Co., Jordan), lactose, starch (Riedel-Dehean, Ag seelze- Hannover, Germany), HCl (BDH chemicals Ltd.,Pool, England), Feldene [R] 20 mg Pfizer capsules

Methods

Solubility Study

Determination of piroxicam solublity

The solubility of piroxicam in 0.1N HCl was measured using standardized shake flask method [14] . In this method 60 mg of the drug was added to 50 ml of 0.1N HCl (saturated solution) [15] and the mixture was shaken at 37°C for 48 hours, filtered through ordinary filter paper and the concentration of piroxicam in the filtrate, following suitable dilution, was assayed spectrophotometrically at 333 nm for piroxicam [16].

Effect of additives on the solubility of piroxicam

Starch, lactose, C.P, CCS, SSG were used to study the effect of additives on the solubility of piroxicam. Certain amounts ranging from 60- 480 mg of one of the above additives was added to a bottle containing 60 mg drug. Manual bottle tumbling was used to prepare simple physical mixture, then 50 ml of 0.1N HCl was added to the mixture to determine the solubility of piroxicam in presence of specific amount of additives by shake flask method as mentioned previously.

Preparation of piroxicam capsules

According to the results of solubility study, six different formulas were prepared, in which proxicam was geometrically triturated with certain amount of one or more of the additives (Table 1). The resultant powder was filled in hard gelatin capsule size 0 as 20mg/capsule.

Table 1: Composition of piroxicam capsules

Ingredients*	Formula Number					
	F1	F2	F3	F4	F5	F6
Piroxicam	20	20	20	20	20	20
Starch	480	---	160	420	---	140
Lactose	---	480	320	---	420	280
SSG	---	---	---	60	60	60
Total	500	500	500	500	500	500

*All ingredients are in milligram

Dissolution studies

The dissolution profiles of the drug alone, encapsulated drug, the prepared capsules and Feldene [R] Pfizer capsules as a reference capsules were studied using apparatus 1 (USP, basket). Dissolution medium was 900 ml 0.1N HCl maintained at 37°C ± 0.1°C and stirred at 50 r.p.m for one hour. Five ml of sample were withdrawn at specified time intervals and were replaced with an equal volume of fresh dissolution medium to maintain sink condition. The samples, following suitable dilution were assayed spectrophotometrically at 333 nm.[16]. All dissolution studies were carried in triplicate

Dissolution data analysis

The dissolution profiles of the prepared formulas were compared using f_2 similarity factor. The similarity factor is a logarithmic reciprocal square-root transformation of the sum of squared error and

is a measurement of the similarity in the percentage of dissolution between two curves.

$$f2 = 50 \times \log\left\{[1 + (\frac{1}{n})\sum(R_t - T_t)^2]^{-0.5} \times 100\right\}$$

Where *n* is the sampling number, R_t and T_t are the percent dissolved of the reference and test products at each time point t. Two dissolution profiles are considered similar when the f_2 value is greater than or equal to 50[17].

Results and Discussion

Effect of additives on the solubility of piroxicam

The effect of type and amount of additives on the solubility of piroxican in 0.1N HCl is summarized in table (2). The solubility of piroxicam was highly improved in presence of the hydrophilic superdisintegrants more than with lactose, a soluble carrier or with starch which have limited solubility and swelling properties. This improvement in solubility can be explained to be due to the surface adsorption of drug in the physical mixtures of all carriers [10]; the wetted surface of the carrier promotes wettability and solubility of the drug [18, 19]. In addition, it was found that within the superdisintegrants, the order of improvement in the solubility is SSG > CCS > C.P which may be due to the differences in their physical properties including hydrophilicity and swelling property. On the other hand, the results in table (2) show that increasing the amount of superdisintegrants results in decreasing the solubility of the drug. This could be attributed to the formation of viscous barrier resultant from absorption of water by the superdisintegrants that decrease the wettability and thus the solubility of the drug [13].

Table 2: Effect of type and amount of additives on the solubility of piroxicam (mg/50 ml) at 37°C in 0.1 N HCl

Amount of Additive (mg)	Type of additives				
	Starch	Lactose	C.P	CCS	SSG
0	6.36 ± 0.46	6.36 ± 0.46	6.36 ± 0.46	6.36 ± 0.46	6.36 ± 0.46
60	6.39 ± 0.02	10.23 ± 0.04	11.47 ± 0.12	13.42 ± 0.01	14.02 ± 0.42
120	7.87 ± 0.25	10.39 ± 0.18	12.51 ± 1.09	12.65 ± 0.15	12.97 ± 0.52
180	10.89 ± 0	11.67 ± 0.17	12.01 ± 0.13	12.05 ± 0.12	12.96 ± 0.2
240	10.88 ± 1.17	12.02 ± 0.52	11.71 ± 1.09	10.88 ± 0.57	11.84 ± 0.31
300	10.97 ± 1.32	12.4 ± 0	----	----	----
360	11.26 ± 0	12.29 ± 0.08	----	----	----
420	11 ± 0.64	12.29 ± 0	----	----	----
480	11.04 ± 0.06	12.16 ± 0	----	----	----

All values are expressed as mean ± standard deviation (n=3)

Preparation of piroxicam capsules

Six different formulas (Table 1) of piroxicam capsules were prepared using starch, lactose or combination of lactose: starch (2:1) by weight [20] with or without the addition 60 mg SSG (the minimum amount among the superdisintegrants that cause the highest solubility) since the presence of any of the above additives have no adverse effect on the solubility of the drug.

Dissolution studies

Effect of gelatin shell

The dissolution of drug from hard gelatin capsule was faster than that from pure powdered drug as shown in figure (1). Pure powdered drug added to dissolution medium remains as agglomerate floats on the surface of the dissolution medium. The enhancement effect of gelatin may be due to its hydrophilic nature that increases wetting and dissolution of the drug. This result can be supported by that obtained by Chono S. *et al* [21] who found that gelatin enhances the dissolution of poorly soluble drugs and their absorption from G.I.T.

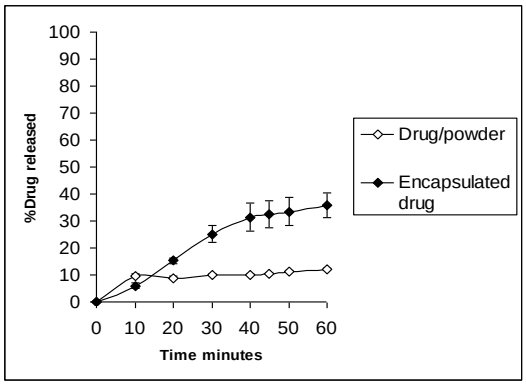

Figure 1: Effect of gelatin shell on the dissolution of piroxicam in 0.1 N HCl at 37°C

Effect of type of diluents

Dissolution profiles of powdered drug, encapsulated drug, and formula (F1, F2 and F3) which contain starch, lactose and lactose: starch (2:1) by weight respectively are shown in figure (2). It is evident that all additives increase the dissolution of the drug. In addition the dissolution profiles of these formulas are not similar. Dissolution profiles comparison (table 3) between F1 and F2 yield f_2 39.75, while dissolution profiles comparison between F2 and F3 yield f_2 48.9. The higher effect was obtained with F2 mainly for the first 20 minutes which is in agreement with the result obtained by Ampolsuk C. *et al* [22] who stated that deposition of hydrophobic drug in a molecular subdivision on excess powdered lactose (due to frictionally prepared triturate) is an effective method of increasing surface of the drug and hence, its dissolution. Since lactose is soluble in simulated gastric fluid, its presence in the dissolution medium would physicall separate drug particles, preventing their agglomeration and enhancing their dissolution. On the other hand, the less enhancing effect of F1 and F3 at the first 20 minutes may be due to the presence of starch which has less solubility in the dissolution medium.

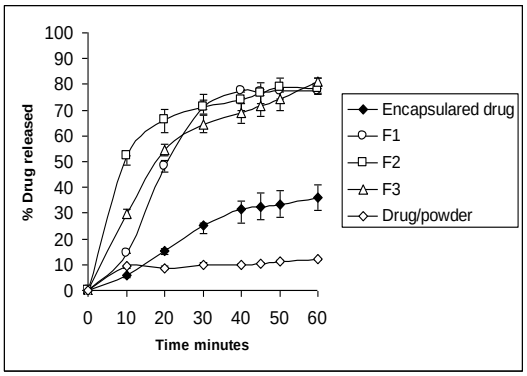

Figure2: Effect of type of diluents on the dissolution of piroxicam in 0.1 N HCl at 37°C

Effect of addition of SSG

Trying to further enhance the release of piroxicam from the prepared capsules, SSG was added in combination with the used diluents to prepare F4, F5 and F6. The dissolution profiles shown in figures 3a and 3c are non similar with f_2 39.17 and 47.47 respectively which indicate that SSG enhances the release of the drug when it is present in combination with starch (F4) or with lactose: starch (2:1) (F6) .On the other hand, combination of SSG with lactose (F5) gives similar dissolution profiles as shown in figure 3b with f_2 59.57, so no further improvement in dissolution . These results indicate that the presence of the SSG in the dissolution medium kept the drug particles in dispersed condition i.e it prevents the agglomeration of drug particles and promote its wetting and dissolution[23] .This action is most effective when it is combined with insoluble or slightly soluble diluents[24], since the water soluble diluents may increase the viscosity of the penetrating fluid which tends to reduce the effectiveness of SSG while the insoluble diluents produce rapid disintegration with adequate of disintegrant [25].

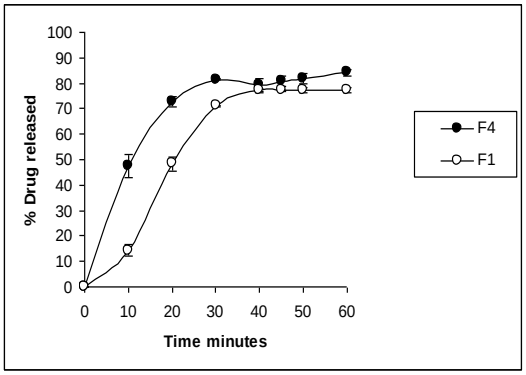

Figure 3.a : Effect of combination of SSG with starch on the dissolution of piroxicam in 0.1 N HCl at 37°C

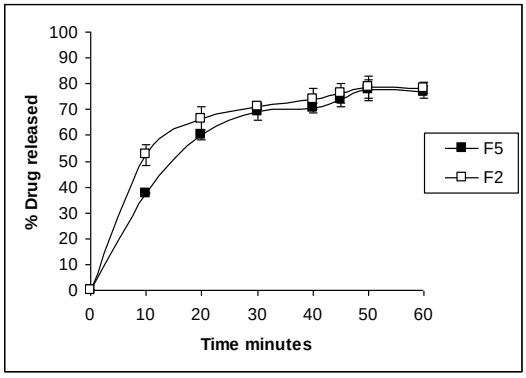

Figure 3.b: Effect of combination of SSG with lactose on the dissolution of piroxicam in 0.1 N HCl at 37°C

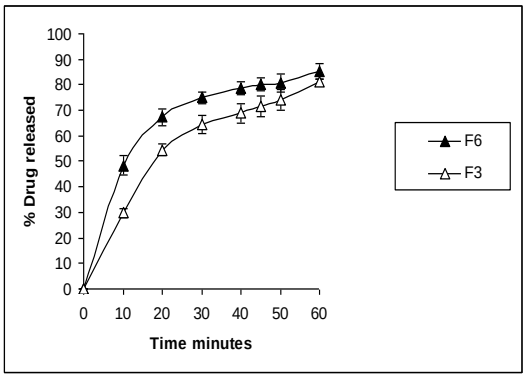

Figure 3.c: Effect of combination of SSG with lactose: starch (2:1) on the dissolution of piroxicam in 0.1 N HCl at 37°C

Comparision of the prepared capsules with the marketed capsule

All the prepared capsules of F1, F2, F4, and F6 met the USP specification for the release of the drug in simulated gastric fluid (not less than 75% of the drug is dissolved in 45 minutes) [16]. The prepared capsules from F4 and F6 which showed fastest dissolution were compared with the marketed Felden [R] Pfizer capsules (figure 4). Similar release profiles were obtained between F4 and Feldene [R] Pfizer capsules yield f_2 74.6, and that between F6 and Feldene [R] Pfizer capsules yield f_2 80.37. In addition, to similar dissolution profiles these preparations contain simple, safe [26], available materials that enhance the solubility and the dissolution of the drug. This gives superiority of using these diluents on sodium lauryl sulfate (a solubilizing agent) that is used in Pfizer product [27]for preparation of piroxcam capsules.

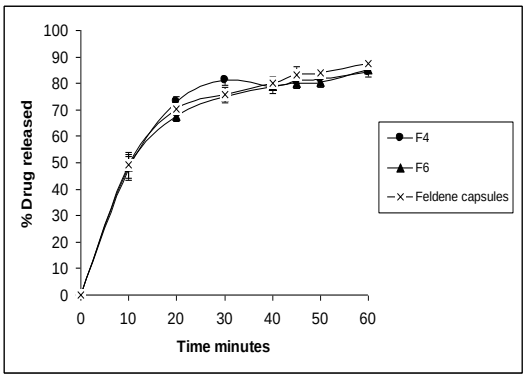

Figure 4: Comparison of the release profile of the prepared capsules with the marketed Feldene [R] Pfizer capsules in 0.1 N HCl at 37°C

Table 3: Values for the similarity factor f_2 for the release profiles in 0.1 N HCl

Formula no.	F2	F3	F4	F5	F6	Felden Cap. Pfizer[R]
F1	39.7504	54.85394	39.17509	49.29237	40.85396	39.12536
F2		48.90846	60.2949	59.57132	68.30451	61.21903
F3			43.99996	66.79376	47.47173	44.28989
F4				51.63288	73.76971	74.60086
F5					56.26644	51.46837
F6						80.37825

Conclusion

The results of this study indicate that the simple physical dry mixing of the piroxicam with starch or with lactose:starch (2:1) by weight in presence of SSG can enhance its solubility as well as its dissolution characteristics to be similar to that of Felden [R] Pfizer . This physical dry mixing of hydrophobic drug with suitable type and amount of additives may be considered as a useful, simple method for preparation of a required solid dosage form. Further work may be required to study the stability of the prepared capsules to investigate its expiration date.

References

1. Amidon G.L., Lennernas, H., Shah, V.P., and Crison, J.R. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm. Res. 1995; 12:413-420
2. Serajuddin A.T.M. Salt formation to improve solubility. Advan.Drug Delivery rev. 2007; 59: 603-616
3. Martindale: The Complete Drug Reference (CD) 2009 .The pharmaceutical press
4. Woolf A.D., Rogers H.J., Bradbrook I.D. and Corless D.Pharmacokinetic observations on piroxicam in young adult, middle - aged and elderly patients. Br.J.clin. Pharmac 1983; 16:433-437
5. Shukla V., Rajashree, M.S., Bolmal, U.B., and Manvi, F.V. Formulation and Evaluation of Piroxicam Dispersible Tablets using Natural Disitegrants. The Indian Pharmacist. 2007;6 : 685-688
6. Javadzadeh Y., Siahi-Shadbad, MR., Barzegar-Jalali M., and Nokhodchi, A. Enhancement of dissolution rate of Piroxicam using liquisolid compacts. Farmaco.2005; 60(4): 361-365.
7. Gwak H.S., Choi J. S, and Choi H. K. Enhanced bioavailability of pirxicam via salt formation with ethanolamine Int. J. Pharm. 2005;297 issues 1-2: 156-161.
8. Tantishaiykul V., Kaewnoppart N., and Ingkatawornwong S. Properties of solid dispersion of piroxicam in polyvinylpyrrolidone K-30.Int.J.Pharm. 1996; 143:59-66.
9. Pan RN., Chen JH. and Chen RRL. Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems. Drug Dev. Ind. Pharm 2000;26: 989-949.

10. Charumanee S., Okonoki S., and Sirithunylug J. Improvement of the dissolution rate of piroxicam by surface solid dispersion CMU. Journal 2004; 3(2): 77-84

11. Bhise S., Chaulang G., Patel P., Patel B., Bhosale A., and Hadihar S. Superdisitegrants as solubilzing agent. Research J. Pharm. and Tech. 2009; 2(2): 387-391

12. Anil R,B., Darwhekar G.N., Nagori V. and Panwar A.S. Formulation and evaluation of fast dissolving tablet of piroxicam. Int. J. Pharm. and Tech. 2011; 3, issue no.2: 2680-2700

13. Bolhuis G.K., Zuurman K. and te Wierik G. H. P. Improvement of dissolution of poorly soluble drugs by solid deposition on a superdisintegrants and effect of granulation. Europ. J. Pharm. Sci. 1997; 5, 1ssue 2: 64-69

14. Mali S. L., Nighute A. B., Deshmukh V. Gonjari I.D., and Bhise S. B. Microcrystals: for improvement of solubility and dissolution rate of lamotrigine. Int. J. Pharm. Sci. 2010; 2(2): 515-521

15. Naseri N. G., Ashnagar A., and Husseini F. Study of inclusion complexation of piroxicam – β – cyclodextrin and determination of the solubility constant (K) by UV- viscible spectroscopy. Scientica Iranica 2007; 14(4): 308-315

16. USP. 30 NF 25 2007

17. Costa P., Lobo J.S. Modeling and Comparison of Dissolution Profiles, European Journal of Pharmaceutical Sciences, 2001; 13,123–133

18. Te Wierik GHB, and Bolhuis GK. Improvement of dissolution of poorly soluble drugs by solid deposition on a superdisintegrants I. Physical mixture. Acta Pharm. Nord 1992; 4:239-244

19. Kalyanwat R., Gupta S., KrSongara R., Jain, D. and Patel, S. Study of enhancement of dissolution rate of Carbamazepine by solid dispersion. IJCP 2011; 2: issue 5.

20. Soebageo S., and Stewart P. The characterization of drug redistribution in a ternary interactive mixture of diazepam. Int. J. Pharm. 1993; 91: 227-233.

21. Chono S., Takeda E., Seki T. and Morimoto K. Enhancement of the dissolution rate and gastrointestinal absorption of pranluast as model poorly-watersoluble drug by grinding with gelatin. Int. J. Pharm. 2008; 374(issue 1-2): 71-78

22. Ampolsuk C., Mauro J. V., Nyhuis A.A., Shah N, and Jarowski C. I. Influence of dispersion method on dissolution rate of digoxin-lactose and hydrocortisone Triturate I. J. Pharm. Sci. 1974; 63(1): 117-118

23. Makiko F., Hideko O. YuSuke S., Honami T. Masuo K. and Yoshiteru W. Preparation, characterization, and tableting of a solid dispersion of indomethacin with crospovidone. Int. J. Pharm. 2005; 293:145-53

24. Product Sheet

25. Chebli C. and Cartlizer L. Cross linked cellulose as a tablet excipient: A binding or disitegranting agent. Int. J.Pharm. 1998; 171: 101-110

26. Pifferi G. and Restani P. The safety of pharmaceutical recipients. Il Farmaco 58 2003; 541_ 550

27. Feldene $^{(R)}$ Pfizer capsules material safety data sheet