ejpmr, 2016,3(12), 74-80

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MICROENCAPSULATION OF PIROXICAM USING PH SENSITIVE POLYMERS

Esmat E. Zein, Ahmed A. Donia and Sania El-kayad*

Faculty of Pharmacy, Pharm. Technology Dept. Tanta University, Tanta, Egypt.

***Corresponding Author: Dr. Sania El-kayad**

Faculty of Pharmacy, Pharm. Technology Dept. Tanta University, Tanta, Egypt.

Article Received on 02/11/2016 **Article Revised on 23/11/2016** **Article Accepted on 13/12/2016**

ABSTRACT

Different techniques are utilized to reduce gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs) including microencapsulation by pH sensitive polymers. Enteric coated piroxicam microspheres were prepared to reduce its side effects. Microspheres were prepared using emulsion solvent evaporation method using Eudragit L_{100} and Eudragit S_{100} as pH sensitive polymers for enteric coating of piroxicam. Entrapment efficiency and percent yield was measured for the prepared formulations and it was found that it depends on polymer type as well as drug polymer ratio. IR analysis was used to predict any interaction between drug and the used polymers. It revealed presence of intermolecular hydrogen bonding between piroxicam and Eudragit polymers. In vitro dissolution test was carried out using three different PH media (1.2, 6.8 and 7.4) to determine release of drug at different pH values. All formulations showed burst release at PH 1.2 but Eudragit L_{100} polymer containing formulations showed the highest initial rapid burst release. Formula B2 was found to be the best formula as it has only 6% burst release within 2 hrs at pH 1.2.

KEYWORD: Eudragit L_{100} and Eudragit S_{100}

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are well known for their gastrotoxic and duodenotoxic effects. A growing proportion of elderly patients require NSAIDs therapy for the treatment of osteoarthritis or rheumatoid arthritis.

Piroxicam is one of the most potent (NSAIDs) used in musculoskeletal as well as joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis.[1] Piroxicam suffers from the same gastrointestinal side effects as all (NSAIDs).

Early studies using pH-sensitive polymers have been interested in pH variation in the gastrointestinal (GI) tract due to the most pronounced and huge pH fluctuation (pH 1~8) in the human body and have focused on the development of controlled delivery formulations for oral administration (e.g., enteric coating materials to protect stomach and/or acid-labile drugs in the stomach, colon specific delivery systems with a pH modulated release property, and taste masking materials for bitter drugs).[2-4]

pH-sensitive polymers are those of which solubility or conformation in aqueous solution is reversibly or irreversibly changeable by environmental pH. They are a class of polyelectrolytes that have ionizable groups in their structures of backbone, side group, or end group and demonstrate pH-dependent physico-chemical properties.[5]

One of the most representative pH-sensitive polymers developed for enteric coating purpose is methacrylic acid copolymers with methyl methacrylate or ethyl acrylate (Eudragits®) that already have a long history of use. Eudragit L_{100} and Eudragit S_{100} are polymers of choice for preparation of pH sensitive microspheres of piroxicam.

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the drug to the target tissue in the optimal amount in the right period of time thereby causing little toxicity as well as minimal side effects. One such approach is using microspheres as carriers for drugs.[6]

The main objective of this research is preparation of piroxicam microspheres using pH sensitive polymers of Eudragit L_{100} and Eudragit S_{100} to reduce its GI side effects.

2. MATERIALS AND METHODS

2.1. Materials

Piroxicam was purchased from Pfizer, New York, USA. Dichloromethane, ethanol, and sodium lauryl sulphate

were purchased from ISO-CHEM Company, China. All other chemicals and reagents were of analytical grade and used as received.

2.2. Methods

2.2.1. Construction of calibration curves

A suitable and accurately weighed quantity of piroxicam was dissolved in methanol to obtain a stock solution.[7] Standard solutions were prepared by dilution of the stock solution with phosphate buffer (pH 6.8, 7.4) and SGF without pepsin (pH1.2). Ultraviolet absorbance of the solutions was determined spectrophotometrically (Thermo, Evo300pc, USA) at the wavelength of maximum absorbance at 354 nm for pH 6.8, 353 nm for pH 7.4 and 334 nm for pH 1.2.[8]

2.2.2. Preparation of piroxicam microspheres

Piroxicam microspheres were prepared by emulsification solvent evaporation method.[9] Drug and Eudragit polymers were used in ratios of 1:1, 1:3 and 1:5 in order to obtain significant different characteristics. Eudragit polymers used were L_{100} and S_{100}. The required amounts of the polymer were dissolved in a mixture of dichloromethane and ethanol (2:3 v/v). The calculated amounts of piroxicam powder were dissolved in the polymeric solutions. The prepared dispersions were slowly poured into 200 ml of 0.2 % w/v sodium lauryl sulphate aqueous solution and were emulsified by vigorous stirring at 1300 rpm at room temperature using magnetic stirrer. The dispersed drug and polymers were immediately transformed into fine droplets, which were subsequently solidified into rigid microspheres due to solvent evaporation.[10] Stirring was continued for 3-4 hrs until all solvent was evaporated. The formed microspheres were allowed to settle, filtered and washed several times with distilled water.[11] The microspheres were dried and stored in air tight containers until further analysis. The compositions of the drug as well as the other additives in addition to the conditions of the preparation are illustrated in Table 1.

Table 1: The composition and the conditions of preparation of different microspheres formulations

Polymer used	Formula No.	Drug :polymer ratio	Stirring rate(rpm)	Surfactant conc.(w/v)	Internal phase volume(ml)	External phase volume(ml)
Eudragit L_{100}	A1	1:1	1300	0.2%	50	200
	A2	1:3	1300	0.2%	50	200
	A3	1:5	1300	0.2%	50	200
Eudragit S_{100}	B1	1:1	1300	0.2%	50	200
	B2	1:3	1300	0.2%	50	200
	B3	1:5	1300	0.2%	50	200

3. Evaluation of the prepared microspheres

3.1. Surface morphology (SEM)

Scanning electron microscopy has been used to determine the surface morphology and texture of the prepared microspheres. A small amount of microspheres was spread on gold stub. Afterwards, the stub containing the sample was placed in the scanning electron microscopy (SEM) chamber. A scanning electron photomicrograph was taken at the acceleration voltage of 25 KV.[12]

3.2. Drug-polymer interaction (FTIR study)

IR spectrophotometer was used to indicate interaction (if any) between drug and polymers. IR spectroscopy was performed using Fourier- transform infrared spectrophotometer, (Jasco, Japan). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning between 4000 and 400 cm-1. FTIR study was carried out on pure drug, Eudragit polymer, physical mixture of drug and polymer as well as prepared microspheres formulations.[13]

3.3. Percentage yield

The prepared microspheres were collected and weighed.[14] The actual weight of obtained microspheres divided by the total amount of all materials that was used for the preparation of the microspheres. Percentage yield of the microspheres was calculated as follow:

% yield of prepared microspheres
= (Actual weight of the product/Total weight of excipients and drug) X 100.

3.4. Entrapment efficiency

The entrapment efficiency (%) of the prepared microspheres was evaluated using the method of Gangadhar *et al.*[15] with certain modification. About 25mg of the obtained microspheres were crushed into powder and were completely dissolved in 100ml of Phosphate buffer solution (pH 7.4) and agitated in a mechanical shaker for 6hrs then kept for 24hrs. Five ml of the obtained solution was filtered then the concentration of the drug was determined spectrophotometrically at 353nm after appropriate dilution.[16,17] The actual drug loading and encapsulation efficiency (EE %) were calculated using the following equations:

Theoretical drug loading (%) = (Drug (total)/ (Drug (total) + polymer) X 100

Actual drug loading (%) = (Drug (entrapped)/ (Drug (total) + polymer) X 100

Encapsulation efficiency (%) = (Actual drug loading/Theoretical drug loading) X 100

3.5. In vitro drug release study

In vitro drug release from the prepared microspheres was performed in different pH media (1.2, 6.8 and 7.4) at 37 ±0.5. The release of piroxicam from microspheres was

determined using type 2 dissolution apparatus (Copley,NG 42JY,Nottingham,UK). Microspheres equivalent to 20 mg were weighed accurately and added to 900 ml of dissolution medium. The contents were rotated at 100 rpm. The pH of the dissolution medium was kept at 1.2 for 2 hrs and 6.8 for 4 hrs then the pH of the dissolution medium was adjusted to 7.4 using 0.1N NaoH and dissolution was continued for another 2 hrs. Five ml samples were withdrawn from the dissolution medium at various time intervals and replaced with 5 ml fresh media to keep sink conditions. The concentration of the drug released was analyzed using UV spectrophotometer.

4. RESULTS AND DISCUSSION

4.1. Entrapment efficiency and percentage yield

The percent entrapment efficiency varies according to different variable parameters such as polymer type and drug to polymer ratio. For polymer type, the higher viscosity of Eudragit S_{100} solution than Eudragit L_{100} leads to the formation of larger droplets under the same stirring conditions and thus less entrapment efficiency. A greater size of Eudragit S_{100} micro particles prepared under the conditions as Eudragit L_{100} micro particles was attributed to the nature of the polymer.[18] The results of entrapment efficiency and percentage yield is illustrated in Table 2.

Table.2: Characterization of piroxicam microspheres

Formula	Entrapment efficiency (%)	Percentage yield (%)
A1	70.94±0.02	90.65±0.3
A2	60.17±0.01	87.35±0.5
A3	50.96±0.03	90.98±0.4
B1	55.42±0.02	80.94±0.3
B2	64.86±0.01	81.57±0.2
B3	58.59±0.01	80.46±0.4

Each result is the mean of 3 determinations ± S.D

From Table 2, it is obvious that Formulations containing Eudragit L_{100} polymer indicates that entrapment efficiency decreases from formula A1-A3 depending on drug to polymer ratio. Increasing polymer concentration increases viscosity of the solution which was responsible for the formation of larger polymer/solvent droplets. It caused a decreased rate of entrapment of drug due to slower hardening of the larger particles allowing time for drug diffusion out of the particles which tends to decrease the encapsulation efficiency.[19] For formula B1-B3 containing Eudragit S_{100} polymer increasing polymer concentration increases encapsulation efficiency until formula B2 then increasing polymer concentration decreases encapsulation efficiency. The contribution of a high polymer concentration to the encapsulation efficiency can be due to better coating of drug resulting from precipitation of polymer on the surface of the dispersed phase which leads to preventing of drug diffusion across the phase boundary. Then further increase in the viscosity of the polymer solution of formula B3 than B2 results in decreasing encapsulation efficiency.

4.2. Scanning electron microscope and IR analyis

Scanning electron microscope results indicate that Eudragit microspheres of piroxicam were successfully prepared using emulsion solvent evaporation method. The prepared microspheres were spherical in shape with voids and pores on its surface due to solvent evaporation as shown in Figure 1.

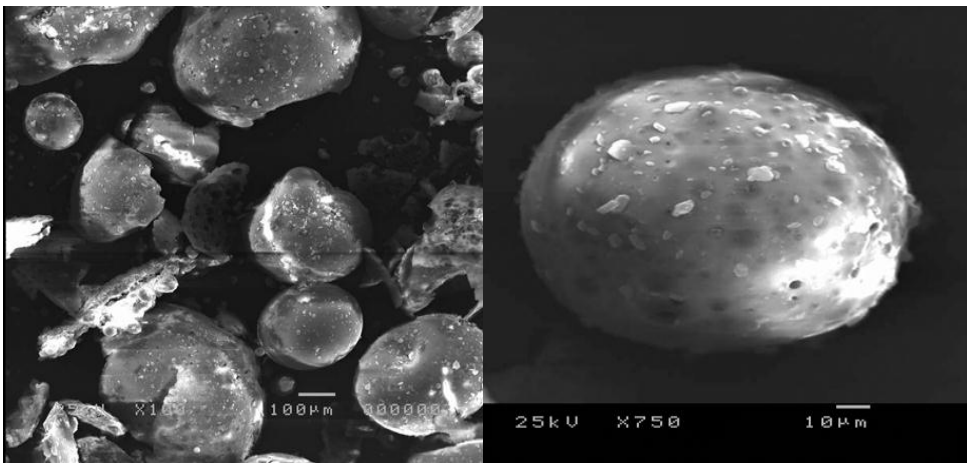

Fig: 1 Scanning electron microphotograph of piroxicam microspheres.

The FTIR spectrum of piroxicam, Eudragit L_{100}, Eudragit S_{100}, physical mixture of piroxicam and Eudragit L_{100} and S_{100} polymers as well as the prepared microspheres are presented in Figure 2. Piroxicam has two possible

tautomeric forms, the 1724 cm^{-1} band was not observed in the obtained IR spectrum suggesting that piroxicam is present in its enol form to interact with intramolecular hydrogen bonding in the piroxicam structure.[20,21] Physical mixture spectrum indicates only the summation of piroxicam and Eudragit polymer spectra revealing that there is no interaction between them. The IR absorption peaks at 1632 cm^{-1} and 1529 cm^{-1} are due to the stretching vibration of the carbonyl group and the second amide band respectively. IR spectrum of Eudragit L_{100} and Eudragit S_{100} shows broad peak at 3463 cm^{-1} and 3500 cm^{-1} respectively due to hydroxyl group stretching vibration which differs according to the difference between the two polymers in the hydroxyl group ratios that gives different possibility in the hydrogen bonding formation. The IR peaks at 1632 and 1529 cm^{-1} of pure piroxicam shifted to 1640 and 1526 cm^{-1} for the piroxicam microspheres respectively. This is due to the carbonyl stretching peak at 1632 cm^{-1} which previously formed the intramolecular hydrogen bond in the piroxicam structure, once the interaction occurred between piroxicam and Eudragit L_{100} or Eudragit S_{100} the intramolecular hydrogen bonding disappeared and the peak at 1632 cm^{-1} shifted to the higher wave number of 1640 cm^{-1}. Moreover, the peak at 1529 cm^{-1} assigned the second amide band of piroxicam shifted to 1526 cm^{-1}, due to the intermolecular interaction between piroxicam and Eudragit polymers. Other new peaks at 1600 and 1329 cm^{-1} also might be due to the complex formation of piroxicam and Eudragit polymers.[22] IR spectrum of piroxicam shows a characteristic peak at 3339 cm^{-1} which may be due to NH or OH stretching vibration while microspheres spectrum of both Eudragit polymers have peak at 3454 cm^{-1} which may indicate presence of intermolecular interaction between piroxicam and the used Eudragit polymers. The results of the IR analysis is presented in (Fig. 2).

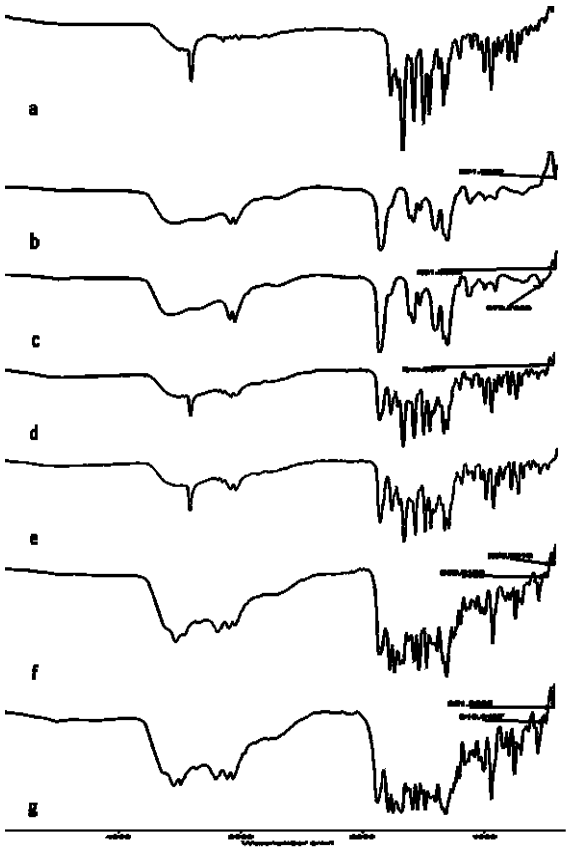

Fig. 2 IR spectrum of (a)piroxicam,(b)Eudragit L_{100} polymer,(c)Eudragit S_{100} polymer,(d)physical mixture of piroxicam and Eudragit L_{100},(e) physical mixture of piroxicam and Eudragit S_{100},(f)prepared piroxicam and Eudragit L_{100} microspheres,(g) prepared piroxicam and Eudragit S_{100} microspheres.

4.3. In vitro release results

Stimuli-responsive polymers show a sharp change in properties upon a small or modest change in environmental condition, e.g. temperature, light, salt concentration or pH. This behavior can be utilised for the preparation of so-called 'smart' drug delivery systems, which mimic biological response behaviour to a certain extent. The possible environmental conditions to be used for this purpose are limited due to the biomedical setting of drug delivery as application. Different organs, tissues and cellular compartments may have large differences in pH, which makes the pH a suitable stimulus. The pH is an important signal, which can be addressed through pH-responsive materials.[23]

pH sensitive polymers named as polyacids or polyanions, such as, poly(acrylic acid) (PAA) or poly(methacrylic) acid (PMAA) are polyanions that have in their structure a great number of ionizable acid groups, like carboxylic acid or sulfonic acid.[24] The carboxylic groups accept protons at low pH values and release protons at high pH values.[25] Thus, when the pH increases the polymer swells due to the electrostatic repulsion of the negatively charged groups. The pH in which acids become ionized depends on the polymer's pKa (depends on the polymer's composition and molecular weight). Thus, in an oral drug delivery system, the poly (acrylic acid) polymer retains the drug on the presence of acid pH (stomach), delivering it in alkaline pH (small intestine). The drug delivery occurs due to the ionization of pendant groups of carboxylic acids, forcing the polymer to swell.[26] Eudragit L_{100} and Eudragit S_{100} are important polymers of these groups.

Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (R). Eudragit polymers are available in a wide range of different physical forms (aqueous dispersion, organic solution granules and powders). To protect the active ingredient from the gastric fluid and to improve drug effectiveness– Eudragit L and S polymers are preferred choice of coating polymers. They enable targeting specific areas of the intestine. In addition, the different grades can be combined with each other, making it possible to adjust the dissolution pH, and thus to achieve

the required GI targeting for the drug. Targeted drug release in the colon is required for local treatment of intestinal disorders such as Crohn's disease, ulcerative colitis or intestinal cancer. It is also required for drugs that are poorly soluble in the upper gastrointestinal tract. Moreover, the gastroresistance of the coating ensures that the oral dosage form is patient compliant.[27]

Eudragit L100 and S_{100} polymer are anionic copolymer based on methacrylic acic and methyl methacrylate which show dissolution at pH 6 and pH 7 respectively. These make them a suitable candidate for preparation of piroxicam microspheres to reduce gastric ulceration side effects of piroxicam.

Dissolution was carried out at different PH media (1.2, 6.8, and 7.4) in order to determine the effect of changing pH on the release of the drug from different microspheres formulations. Piroxicam shows different solubilities at different pH values as its solubility is pH dependent (Fig. 3).

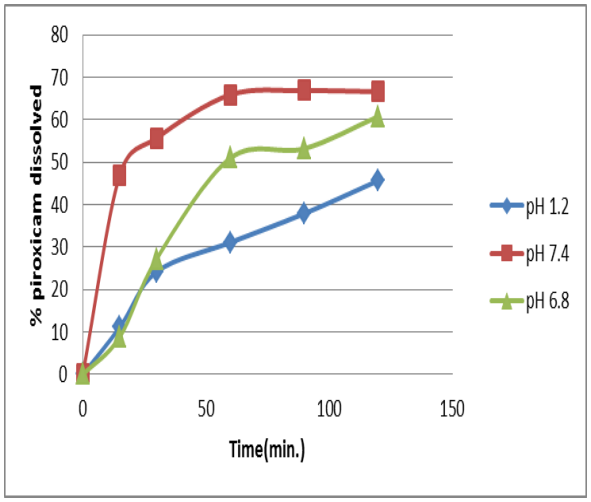

Fig.3. Dissolution profiles of piroxicam in a free form at different pH values.

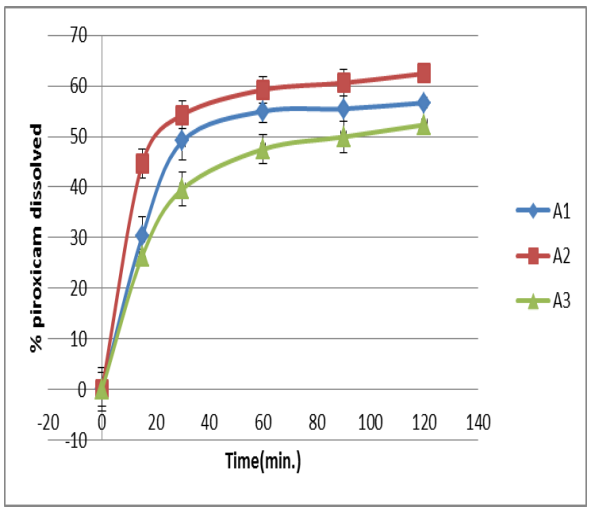

Fig.4. Dissolution profiles of piroxicam from its microspheres of different formulations of eudragit L_{100} polymer at pH 1.2.

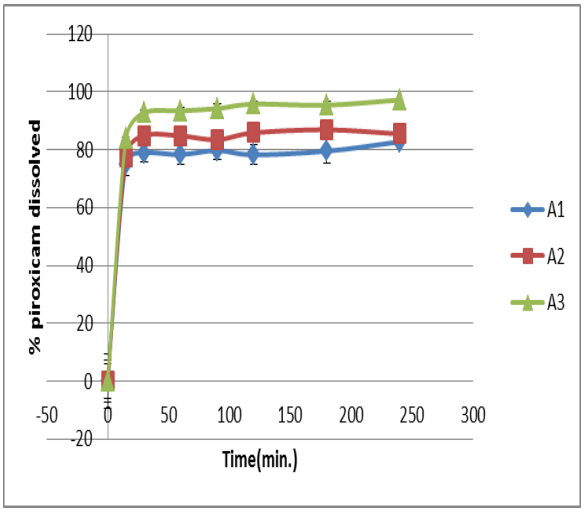

Fig.5. Dissolution profiles of piroxicam from its microspheres of different formulations of eudragit L_{100} polymer at pH 6.8.

The in vitro release of the drug from the microspheres prepared by the solvent evaporation method was reported to be biphasic in nature and rapid with a burst effect.[28] Eudragit L_{100} formulations show initial rapid burst release with more than 50% of drug released within 2 hrs at pH 1.2 (Fig.4). At pH 6.8 there is a rapid release of the drug as more than 75% released after 15 min. Formula A3 shows the highest amount released of the drug while A1 has the least amount released depending on drug to polymer ratio (Fig.5).

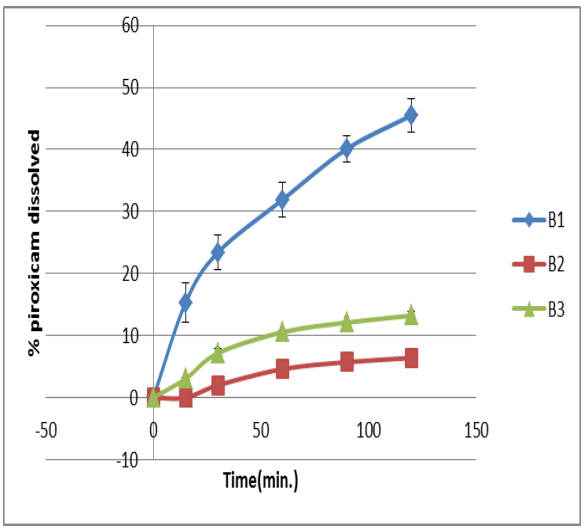

Fig.6. Dissolution profiles of piroxicam from its microspheres of different formulations of eudragit S_{100} polymer at pH 1.2.

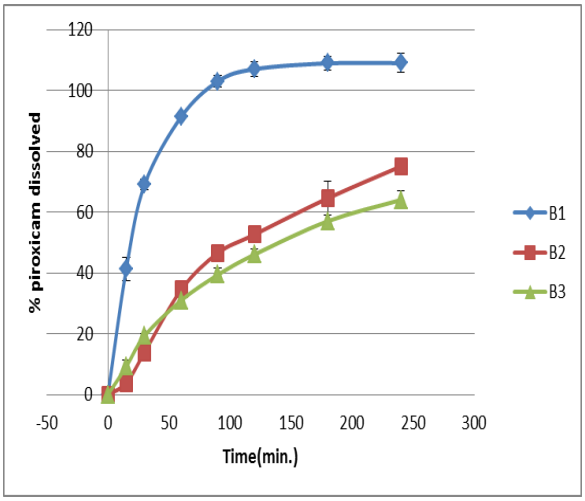

Fig.7. Dissolution profiles of piroxicam from its microspheres of different formulations of eudragit S_{100} polymer at pH 6.8.

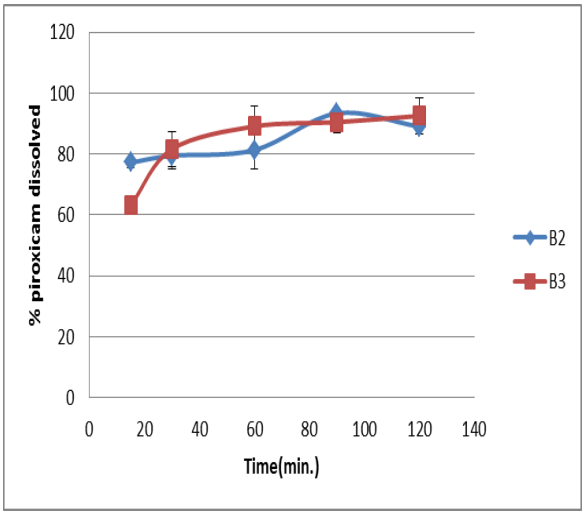

Fig.8. Dissolution profiles of piroxicam from its microspheres of different formulations of eudragit S_{100} polymer at pH 7.4.

For Eudragit S_{100} formulations, formula B1 shows about 45% initial rapid burst release within the first 2 hrs at pH 1.2 then at PH 6.8 release increase rapidly to reach about 91% after 1 hr. Formula B3 has about 13% burst release at pH 1.2 at first 2 hrs then at pH 6.8 the release continue to reach 64% for another 4 hrs. Release of formula B3 lasts for another 2hrs at pH 7.4 to reach 92%. Formula B2 has the best coating and the highest entrapment efficiency of Eudragit S_{100} formulations as it shows only 6% burst release at pH 1.2 after 2hrs which make it the best formula due to the small amount of piroxicam released at gastric pH causing the least side effects of ulceration. Formula B2 also lasts for 8 hrs to reach 89% at pH 7.4 as shown in Fig. (6-8). Eudragit S_{100} microspheres formulations show less burst effect than Eudragit L_{100} microspheres formulations.

5. CONCLUSION

Enteric coated microspheres of piroxicam using Eudragit L_{100} and Eudragit S_{100} were prepared using emulsion solvent evaporation technique in order to reduce its gastrointestinal side effects. Entrapment efficiency and percent yield were measured to evaluate the prepared formulations. IR analysis indicated presence of intermolecular hydrogen bonding between drug and Eudragit polymers. All formulations showed burst release at pH 1.2 during in vitro dissolution test except for formula B2 which show only 6% burst release within 2 hrs at pH 1.2 so it is considered the best formula.

6. REFERENCES

1. Insel, P.A., Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of rheumatoid arthritis and gout. In: Gilman, A.G., Rall, T.W., Nies, A.S., Taylor, P. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, vol. 1. McGraw-Hill, Singapore, 1991; 668–669.
2. Dong L-C and Hoffman A.S. Pharmaceutical Applications of Polymers for Drug Delivery. *J. Control Release*, 1991; 15, 141.
3. Qiu Y and Park K. Environment-sensitive hydrogels for drug delivery. *Adv. Drug Deliv. Rev.*, 2001; 53(3): 321-339.
4. Ayenew Z, Puri V, Kumar L, and Bansal A.K. Trends in pharmaceutical taste masking technologies: a patent review. *Recent Pat. Drug Deliv. Formul*, 2009; 3(1): 26-39.
5. Kang Moo Huh, Han Chang Kang, Young Ju Lee, and You Han Bae. pH-Sensitive Polymers for Drug Delivery. Macromolecular Research, 2012; 20(3): 224-233.
6. Nitika Agnihotri, Ravinesh Mishra,Chirag Goda, Manu Arora. Microencapsulation – A Novel Approach in Drug Delivery: A Review. Indo Global Journal of Pharmaceutical Sciences, 2012; 2(1): 1-20.
7. US Pharmacopeia, 24, US Pharmacopeial Convention, Rockville, MD, 2000: 1342.
8. Ays¸ egül Karatas¸ Nilüfer Yüksel, Tamer Baykara.Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol. Il Farmaco, 2005; 60: 777–782.
9. Mao S, Shi Y, Li L, Xu J, Schaper A and Kissel T. Effect of process and formulation parameters on characteristics and internal morphology of poly (D, L-lactide-co-glycolide) microspheres formed by the solvent evaporation method. Eur. J. Pharm. Biopharm, 2008; 68: 214- 223.
10. Trivedi P, Verma A. M. L and Garud N. Preparation and characterization of aceclofenac microspheres. Asian J. Pharm, 2008; 2: 110-115.
11. Deveswaran R, Manavalan R, Madhavan V and Bharath S. Formulation and Optimization of Ketoprofen Microspheres using Response Surface Methodology. Int. J. PharmTech. Res., 2010; 2(4): 2319-2326.

12. Sandeep S. Formulation and evaluation of colon targeted drug delivery of an anti-amoebic drug. Int J Pharm Innov., 2012; 2(2): 138-152.
13. Ebtessam A. Essa, Fatma E. Elkotb, Esmat E. Zin Eldin, Gamal M. El Maghraby. Development and evaluation of glibenclamide floating tablet with optimum release. Journal of drug delivery science and technology, 2015; 27: 28-36.
14. Chandiran IS, Sivakumar T, Kumar BP. Preparation and evaluation of aceclofenac loaded biodegradable microspheres. Int J Pharm Biomed Res., 2010; 1(1): 19-23.
15. Gangadhar C. B., Sunder S. R., Vimal K.V. M, Raju S. M. and Kiran S. M. Formulation and Evaluation of Indomethacin Microspheres using natural and synthetic polymers as Controlled Release Dosage Forms. Int. J. Drug Dis., 2010; 2(1): 8-16.
16. Marwa H. Abdallah, Omaima A. Sammour, Hanaa A. El-ghamry, Hanan M. El-nahas and Waleed Barakat. Development and characterization of controlled release ketoprofen microspheres. Journal of applied Pharmaceutical Science, 2012; 02(03): 60-67.
17. Yerriswamy B, Reddy C. L. N, Prasad C. V, Subha M. C. S, Rao K. C. and Venkatareddy G. Controlled release studies of 5- fluorouracil through poly (vinyl caprolactum-co- vinyl acetate) microspheres. Asian J. Pharm., 2010; 4(3): 200-204.
18. Kendall R, Alhnan MA, Nilkumhang S, Murdan S, Basit AW. Fabrication and in vivo evaluation of highly pH-responsive acrylic microparticles for targeted gastrointestinal delivery. Eur J Pharm Sci., 2009; 37: 284-290.
19. Das MK, Ramarao K. Microencapsulation of Zidovudine by double emulsion solvent diffusion technique using ethylcellulose. Indian J Pharm Sci., 2007; 69: 244–50.
20. Fernandez M, Rodriguez I.C, Margarit M.V and Cerezo A. Characterization of solid dispersions of piroxicam/polyethylene glycol 4000. Int.J. Pharm., 1992; 84: 197-202.
21. Mihalic M, Hofman H, Kuftinec J, Krile B, Caplar V, Kajfez F and Blazevic, N. Piroxicam. Anal. Profiles Drug Substances, 1986; 15: 509-531.
22. Shari--Yang Lin, Chau-Jen Lee, Yih-Yii Lin. Drug-polymer interaction affecting the mechanical properties, adhesion strength and release kinetics of piroxicam-I oaded Eudragit E films plasticized with different plasticizers. Journal of controlled release, 1995; 33: 375-381.
23. Dirk Schmaljohann. Thermo- and pH-responsive polymers in drug delivery Advanced Drug Delivery Reviews, 2006; 58: 1655–1670.
24. Grainger ST and El-Sayed MEH. Stimuli-sensitive particles for drug delivery. biologically-responsive hybrid biomaterials: a reference for material scientists and bioengineers. World Scientific Publishing Co. Pte. Ltd., Danvers, 2010: 171-189.
25. Gil E.S., Hudson S.M. Stimuli-responsive polymers and their bioconjugates. Prog. Polym. Sci., 2004; 29(12): 1173-1222.
26. Hugo Almeida, Maria Helena Amaral and Paulo Lobão. Temperature and pH stimuli-responsive polymers and their applications in controlled and self-regulated drug delivery. Journal of Applied Pharmaceutical Science, 2012; 02(06): 01-10.
27. Abhijit Sonje, Amrish Chandra.Comprehensive review on eudragit polymers. International research journal of pharmacy, 2013; 4(5): 71-74.
28. Guiziou B, Amstrong D.J, Elliot P.N.C, Ford J.L, Rostron C. Investigation of in-vitro release characteristics of NSAID-loaded polylactic acid microspheres. J. Microencapsul, 1996; 13: (701–708).