academicJournals

Vol. 7(16), pp. 838-847, 29 April, 2013
DOI 10.5897/AJPP12.287
ISSN 1996-0816 © 2013 Academic Journals
http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Preparation and evaluation of sustained release pellets of Tramadol

Nasim Sadri Alamdari[1,2], Zahra Jafari Azar[1], Jaleh Varshosaz[3], Solmaz Ghaffari[1,3,4,5]*, Sanaz Ghaffari[6] and Farzad Kobarfard[7]

[1]Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Islamic Azad University, Pharmacy Branch, Tehran, Iran.
[2]Quality Control Department, Jaber Ebne Hayyan Pharmaceutical Co. Tehran, Iran.
[3]Department of Pharmaceutics, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
[4]Quality Control and R&D Departments, Iranian Parenteral and Pharmaceutical Co (I.P.P.C) Tehran, Iran.
[5]Young Researcher Club, Pharmacy Faculty, Islamic Azad University of Medical Sciences, Tehran. Iran.
[6]Faculty of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran.
[7]Department of Medicinal Chemistry, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Accepted 21 May, 2012

Preparation of sustained release dosage forms is one of the main objectives in drug formulation. Tramadol is a centrally acting synthetic opioid analgesic used in treating severe pain. In this study, Tramadol sustained release pellets were prepared using two methods and the effect of type, ratio of polymers and plasticizers on drug loading and drug release profile was studied. From the results obtained, it seems that Eudragit RL is not a suitable choice and when Tween was used as plasticizer. Moreover, when mixture of Eudragit S and RS were applied as polymers, the optimum drug release profile was obtained and after 10 h, 95% of loaded drug was released.

Key words: Eudragit, Tramadol, sustained release, plasticizer, pellet.

INTRODUCTION

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit typically consisting of thousands of spherical particles with diameter of 0.05 to 2.00 mm. Thus multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits (Dey et al., 2008). Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. Some other studies were done to investigate pharmacokinetics of sustained release dosage forms prepared using ion exchange resins (Liu et al., 2012). Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems (Laila and Chandran, 2006; Hu et al., 2006).

Multiparticulates may be prepared by several methods. Some of these methods may be broadly classified as pelletization, granulation, spray drying, and spray congealing (Bechegaard and Nielson, 1978). Pelletized delivery system (PDS) is a sustained release system using pellets or beads manufactured using marumerization/ spheronization/ pelletization techniques, or by layering powders or solutions on nonpareil seeds

*Corresponding author. E-mail: ghafari@pharm.mui.ac.ir or soligh@yahoo.com. Tel: +98 21 88275524, +989125272146. Fax: +98 21 55543301.

(Dey et al., 2008; Hu et al., 2006) and controlled drug release systems can be assembled from either polymers or pumps. Because of their small size and lower cost, polymers are most widely employed (Garala et al., 2009). Pelletization is a technique that enables the formation of spherical beads or pellets. These pellets can eventually be coated and very often used in controlled-release dosage forms (Hirjau et al., 2011).

Pelletization methods used in the pharmaceutical industry can be grouped by various criteria, e.g. by the type of equipment used, the intensity of the mechanical forces involved or the techniques employed for the production of pellets. The success of these methods depends on the complex relations between the equipment, the formulation and process variables (Hirjau et al., 2011; Bechegaard and Nielson, 1978). Different pelletization methods are as follows:

(a) Extrusion / spheronization (Liew et al., 2000; Ghai et al., 2009; Zhang et al., 2012).
(b) Fluid-bed Granulation.
(c) Rotogranulation is one of the most recent methods for the production of spheroids.
(d) Layering a suspension or a solution of a drug on a seed material.
(e) Dry powder layering is some method in which process is similar to the solution or suspension layering.
(f) Spray-drying represents another process.
(g) Spray-congealing (spray-chilling) is a technique similar to spray-drying (Schaefer and Kristensen, 1993; Bechegaard and Nielson, 1978; Haritha, 2012).

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic used in treating severe pain. The drug has a wide range of applications, including treatment for rheumatoid arthritis, restless legs syndrome and fibromyalgia. Tramadol comes in many forms, including capsules, tablets, suppositories, effervescent tablets, powders, and ampoules for subcutaneous injection (SC), intra-muscular injection (IM), and intravenous (IV) injection and liquids (Trease, 1964). In this study, sustained release pellets of Tramadol were prepared using two different methods and in addition to comparing the suitability of designed methods, the effect of type of polymers, ratio of polymer to drug as an important factor which was studied in other sustained release formulations (Jan et al., 2012), type of emulsifiers, amount of used emulsifiers and core particle size on drug loading and drug release profile were studied.

MATERIALS AND METHODS

Tramadol hydrochloride (Figure 1) was purchased from Palace, Italy. Eudragit RS100, S, L and RL were purchased from Rohm Pharma, Germany. Sucrose, polyvinylpyrrolidone (PVP), isopropanol, acetone, ethanol, polyethylene glycol 400 (PEG 400), Tween 20 and 40, potassium hydrogen phosphate, sodium hydroxide, talc, titanium dioxide and acid chloride were purchased from Merck, Germany.

Preparation of pellets

For preparation of pellets in this study, two different methods were applied. In the first method, primary cores were designed using sieved sucrose and the addition of PVP suspension in isopropyl alcohol, and then the suspension of other components including: calcium carbonate, talc, titanium dioxide and corn starch in water. The prepared cores were separated by sieving method using a sieving machine (Teb Azma, Iran), after which loading of drug was done on the cores and finally polymers were used to coat designed drug loaded pellets. This method was designed to prepare spherical core with high ratio of surface to volume and to increase probability of more drug loading efficiency on them. For this approach, sucrose was sieved using sieves with 16 - 50 mesh size and the fraction of sucrose that remained on sieve with 40 mesh size was chosen to be as core. Table 1 shows the US standard for relation of mesh size and particle size that was applied in this study. From the table, sucrose was 420 micron in size. Three different formulations for first layer were designed and added to sucrose to reach more spherical cores in shape and to protect sucrose as a core. Tables 2 to 5 show different suspension of the first layer on sucrose. For loading of drug on the designed cores, mixture of drug and excipients was sprayed on cores using hand spray gun and coating pan (Erweka, Germany) in different steps to load enough drug. Although some other studies investigated the effect of different experimental parameters on characterization of microcapsules (Esposito et al., 2000), in this study experimental parameters fixed and the effect of presented parameters like ratio and type of polymers and solvents were studied. Tables 6 to 9 show the drug and different polymers in different ratio mixture that were sprayed on the cores to prepare controlled release pellets.

In second method for the preparation of cores, mixture of drug and excipients were used instead of sucrose, using pelletiser (Pelletiser GTE, Erweka, Germany) and then polymers were added to the surface of desired pellets. For preparation of pellets based on the second method, first mixture of drug and some excipients were poured into the pelletiser to make primary cores as it is shown in Table 10. As for the first layer, solution of PVP (10%) in ethanol was sprayed on the desired cores to help powders to adhere to each other and make cores. The second layer was formulated as described in Table 11 and sprayed to the surface of the cores. Desired cores were sieved with sieve sizes of 16 - 40. The cores remaining on the sieve size 20 and 25 were selected and mixed to continue the study. Also, cores remaining on sieve size 18 were separately collected for further studies. Then formulations as described in Tables 12 and 13 were prepared to spray on selected cores. Finally, analyses of desired pellets were done.

Determination of λ max of Tramadol

Absorbance of serial dilution of Tramadol in water and phosphate buffer solution (PBS) pH: 6.8 were studied to determine λ max of Tramadol.

Drug loading efficiency

Briefly, 100 mg of cores and 100 mg pellets containing drug were weighed separately, extruded and dissolved in 100 ml purified water. Pure cores solution was used as blank and Tramadol assay was done in detected λ max.

Drug release study

Dissolution test was done at a desired condition as follows: medium of dissolution was 500 ml water, apparatus number I, 100 RPM at

Table 1. US standard for relation between mesh size of sieves and particle size of materials.

US standard	
Mesh size	**Particle size (µ)**
10	2000
12	1680
14	1410
16	1190
18	1000
20	840
25	710
30	590
35	500
40	420
45	350
50	97

Table 2. Component of formulation 1 that applied as first layer on sucrose core in the first method.

Material	Percentage (%)
Sucrose	50
Talk	10
Calcium carbonate	10
PVP	1
Titanium dioxide	0.5
Water	Up to 100

Table 3. Component of formulation 2 that applied as first layer on sucrose core in the first method.

Material	Amount (g)
Sucrose	35
Calcium carbonate	30
Talk	5
PVP	1
Titanium dioxide	0.5
Corn starch	10
water	30

37.5±0.5°C. The sampling interval was 1 h, in each interval 5 ml samples was gathered and fresh medium was replace. The medium of dissolution for pellets containing Eudragit S and L was changed to HCL 0.1 N for the first 2 h and then PBS, pH:6.8 because these Eudragits are pH sensitive.

RESULTS AND DISCUSSION

Calibration curve of tramadol in water and PBS

The λ max of 272 nm was selected for Tramadol and

Table 4. Component of formulation 3 that applied as first layer on sucrose core in the first method.

Material	Amount (g)
Sucrose	35
Calcium carbonate	30
Talk	8
PVP	1
Titanium dioxide	0.5
Corn starch	10
Water	35
Ethanol	5-10%

Table 5. Components of tramadol containing solution which was sprayed on the cores in firs pellet preparation method.

Material	Amount
Tramadol HCL	5 (g)
Eudragit RS100	5(g)
TEC	15%
Ane	50 (ml)
Ethanol	50 (ml)

calibration curve was designed as shown in Figure 2. The R2 of the both curves was 0.999.

Drug loading on pellets

The amount of drug loaded on the desired pellets is shown in Table 14. According to the results, formulations F1, 5, 7, 8, 10 and 11, F13 to 16 and also F19-21 and 24 had drug loading more than 11%.

Drug release

Figure 3 shows drug release profile of pellets that was studied in water medium. As shown, formulation number 5, 7 and 9 had a significant burst effect and more than 50% of loaded drug was released through them in the first hour. In formulation F8, at the first sampling time, 81% of loaded drug was released and no significant change was observed in 8 h (data not shown). Study of drug release profile through desired pellets showed that usage of polymeric mixture with concentration of 90% Eudragit RS and 10% Eudragit S could be suitable formulation to design sustained release pellets. Usage of total electron content (TEC) and Tween 40 in ratio of 20 to 5%, respectively in coating solution could cause the preparation of pellets with spherical shape, reasonable drug loading and sustained drug release profile. Figures 3 to 5 show the drug release profile; comparison of F1 –

Table 6. Formulations of pellets which containing Eudragit RS.

Formulation number	Ratio of polymer to drug	Acetone (ml)	Ethanol (ml)	Tween 20 (g)	PEG 400	TEC (g)	Eudragit RS (g)
F1	0.25	50	50	-	-	0.75	5
F2	0.27	50	50	-	-	0.75	5
F3	0.39	50	50	-	-	0.75	5
F4	0.88	50	50	-	-	0.75	5
F5	0.25	50	50	-	0.75	-	5
F6	0.30	50	50	-	0.75	-	5
F7	0.20	50	50	0.75	-	-	5
F8	0.26	50	50	0.75	-	-	5
F9	0.31	50	50	0.75	-	-	5

Table 7. Formulations of pellets which containing Eudragit RS and S.

Formulation number	Ratio of polymer to drug	Acetone (ml)	Ethanol (ml)	Tween 20 (g)	TEC (g)	Eudragit S (g)	Eudragit RS (g)
F10	0.3	50	50	-	0.75	0.5	4.5
F11	0.35	50	50	-	0.75	0.5	4.5
F12	0.45	50	50	-	0.75	0.5	4.5
F13	0.20	50	50	0.25	1	0.5	4.5
F14	0.31	50	50	0.25	1	0.5	4.5
F15	0.36	50	50	0.25	1	0.5	4.5
F16	0.44	50	50	0.25	1	0.5	4.5
F17	0.70	50	50	0.25	1	0.5	4.5
F18	0.76	50	50	0.25	1	0.5	4.5

Table 8. Formulations of pellets which containing Eudragit RS and L.

Formulation number	Ratio of polymer to drug	Acetone (ml)	Ethanol (ml)	TEC (g)	Eudragit L(g)	Eudragit RS (g)
F19	0.36	50	50	0.75	0.5	4.5
F20	0.40	50	50	0.75	0.5	4.5
F21	0.45	50	50	0.75	0.5	4.5
F22	0.47	50	50	0.75	0.5	4.5
F23	0.55	50	50	0.75	0.5	4.5

Table 9. Formulations of pellets which containing Eudragit RL.

Formulation number	Ratio of polymer to drug	Acetone (ml)	Ethanol (ml)	TEC (g)	Eudragit RL (g)
F24	0.28	50	50	0.75	10
F25	0.31	50	50	0.75	10
F26	0.42	50	50	0.75	10
F27	0.51	50	50	0.75	10

Table 10. Materials which used to prepare primary cores based on second method.

Material	Amount (g)
Tramadol HCL	10
Lactose	20
Corn starch	20
PVP	2.5

Table 11. Materials which used as second layer to prepare pellets based on second method.

Material	Amount (g)
Sucrose	25
Calcium carbonate	30
Talk	8
PVP	2
Titanium dioxide	0.5
Corn starch	15
Water	30
Ethanol	30

Table 12. Materials used to spray on cores of second method with size of 710-840 µ.

Formulation no	Eudragit RS (g)	Eudragit S (g)	TEC (g)	Tween 40 (g)	Ethanol (ml)	Acetone (ml)	Ratio of polymer to drug
F'13	4.5	0.5	1	0.25	50	50	0.20
F'14	4.5	0.5	1	0.25	50	50	0.30
F'15	4.5	0.5	1	0.25	50	50	0.36
F'16	4.5	0.5	1	0.25	50	50	0.45
F'17	4.5	0.5	1	0.25	50	50	0.70

Table 13. Materials used to spray on cores of second method with size of 1000 µ.

Formulation no	Eudragit RS (g)	Eudragit S (g)	TEC (g)	Tween 40 (g)	Ethanol (ml)	Acetone (ml)	Ratio of polymer to drug
F"14	4.5	0.5	1	0.25	50	50	0.30
F"15	4.5	0.5	1	0.25	50	50	0.35
F"16	4.5	0.5	1	0.25	50	50	0.44
F"17	4.5	0.5	1	0.25	50	50	0.70
F"18	4.5	0.5	1	0.25	50	50	0.75

Table 14. Results of drug loading on pellets.

Formulation no.	Amount of drug (mg %)
F1	11.06 ± 0.079
F2	10.91 ± 0.089
F3	9.47 ± 0.369
F4	8.21 ± 0.373
F5	11.06 ± 0.195
F6	10.74 ± 0.130
F7	11.39 ± 0.284
F8	11.01 ± 0.079
F9	10.47 ± 0.065
F10	12.13 ± 0.073
F11	11.56 ± 0.186
F12	10.97 ± 0.146
F13	12.62 ± 0.075

Table 14. Contd.

F14	12.06 ± 0.107
F15	11.48 ± 0.132
F16	11.1 ± 0.064
F17	8.89 ± 0.2407
F18	7.89 ± 0.140
F19	12.32 ± 0.167
F20	11.95 ± 0.188
F21	11.63 ± 0.193
F22	10.98 ± 0.293
F23	10.64 ± 0.603
F24	11.25 ± 0.117
F25	10.82 ± 0.172
F26	10.52 ± 0.186
F27	10.14 ± 0.235

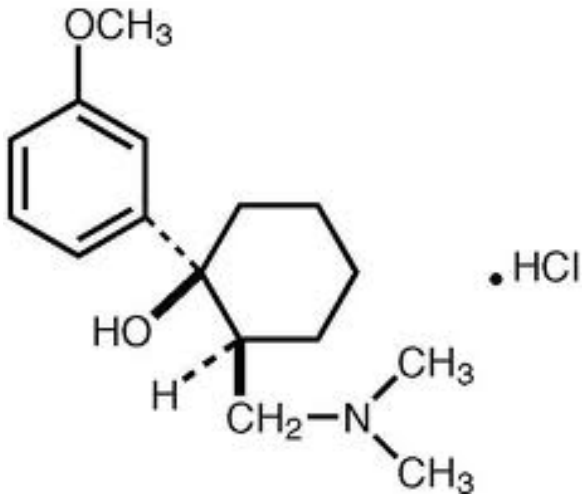

Figure 1. Chemical structure of Tramadol HCL.

F4 shows that in these formulations, increasing the ratio of polymer reduces the amount of drug release, especially at first release times. Comparison of F1, F5 and F8 shows that different plasticizers may cause different drug release profile; all parameters were equal in these formulations and just the type of plasticizer was changed. The desired changes showed that TEC with hydrophobic character could be responsible for less drug release in formulation F1 versus Tween with hydrophilic character, which used in F8 and led to more drug release.

Furthermore, in F5 with PEG as a plasticizer, release profile shows intermediate condition in comparison with F1 and F8. Comparison of F2, F6 and F9 shows the same results. TEC was selected as a better plasticizer to achieve pellets with steady release condition and no significant burst effect. Regarding the drug release results, it seems that Eudragit RS and Tween in legal ratio of polymer usage could not help to design controlled release formulation and most of the drug was released at the first sampling times.

Study on drug release profile of F10 - 12 in which just ratio of polymer was increased, shows that increasing polymer could sustain the release profile and when mixture of Eudragit RS and S was used; results were more reasonable. A study of F19 - 23 shows that formulations which were prepared using mixture of Eudragit RS and L were not suitable to prepare pellets with predicted drug release profile. Based on F24 – 27 we estimated that usage of Eudragit RL could cause higher range of drug release at initial sampling point. Comparison of Eudragit RS with RL shows that ammonium groups in Eudragit RL are more than RS and this reason causes more solubility of Eudragit RL in equal ratio. The formulation containing Eudragit RS could retain the release of drug more than Eudragit RL. These two types of Eudragit are not pH dependent. In comparison of Eudragit S and L, Eudragit S could release drug in pH ranges more than 7 and this range for Eudragit L is more than 6. Hence, Eudragit S could be use as polymer for colon drug delivery and the drug release through it is more sustained. To compare the effect polymer type on drug release profile, formulations F3, 11, 20 and 26 were studied in which the amount of polymers was 0.4 and formulations contained Eudragit RS, mixture of RS and S, RS and RL, respectively. Results showed that more water permeability and more solubility of Eudragit RL does not mean that it will be a suitable polymer for sustained drug release. The sustainability of these Eudragit was in the condition as shown: Mixture of S and RS > RS > mixture of RS and RL > RL. Therefore, the study was continued using mixture of Eudragits S and RS.

In addition, based on the results of plasticizers which were used (TEC, PEG 400 and Tween), TEC as an insoluble plasticizer could cause more sustained formulations. More studies showed that the best condition to achieve formulation with desired drug release profile will be when the mixture of Eudragit S and RS in of ratio of 90, 10 and the mixture TEC and Tween in ratio of 20, 5 were applied. Formulations F13 - 16 had such a condition. In comparison, F16 showed more reasonable drug release profile and drug release profile was studied for 10 h on it; Figures 6 and 7 shows the result. Studies showed that the kinetic of drug release through formulation F16 matched with zero order. The R2 of zero, first and Higushi kinetic was 0.963, 0.910 and 0.955, respectively.

Previous studies have been done to evaluate the ratio of different kinds of Eudragits on the *in vitro* release profile of drug (Hu et al., 2006; Bidah and Vergnaud, 1991; Golman and Jalilpak, 2008; Yadav and Jain, 2011; Adibkia et al., 2012). Some studies showed that the combination of two different acrylic polymers showed better effect on the release kinetics of drug than any individual polymer coated pellets to sustain the release of

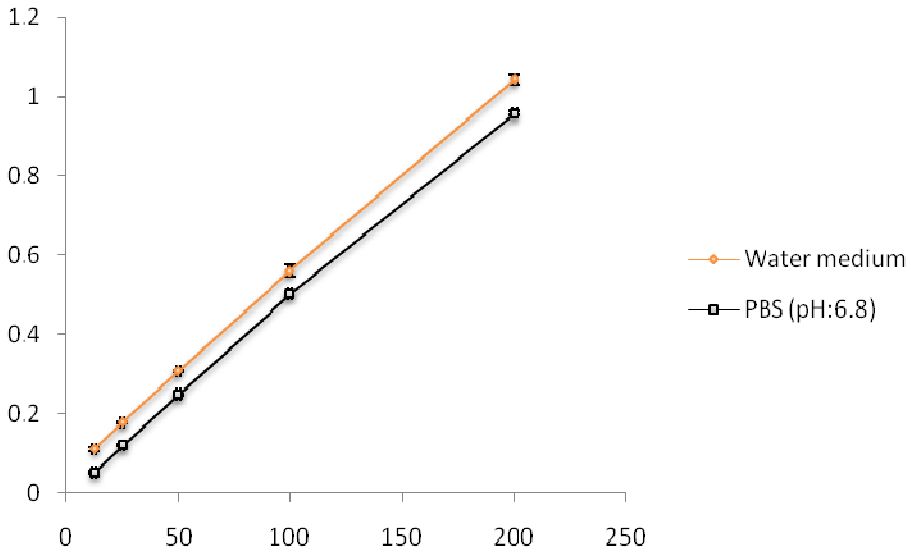

Figure 2. Calibration curve of Tramadol in water in λ_{max}:272 nm.

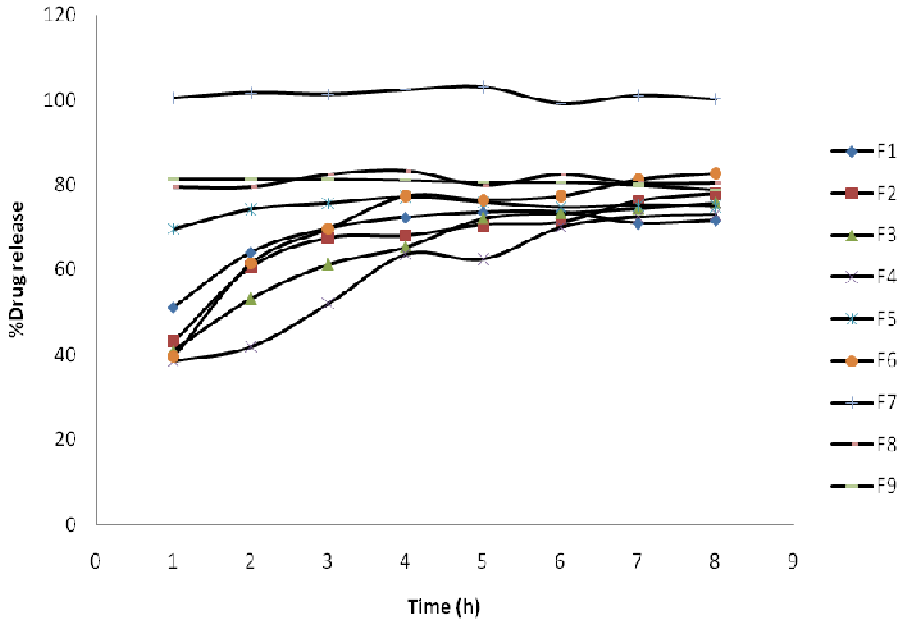

Figure 3. Drug release profile through formulation F1 - F9 in water medium.

drug over a period of time, with better dissolution profile as well as better linearity in drug (ketoprofen) release kinetics (Golman and Jalilpak, 2008). Some other studies showed that when Eudragites were used in formulation, results were affected by the type and ratio of used Eudragit S and also the solvents in which Eudragit RL and RS were suggested to prepare sustained release microcapsules (Kibria and Jalil, 2008; Ghaffari et al., 2011). Compatibility of Eudragits with tramadol was established before by Shinde et al. (2008).

Conclusion

The polymers used in this study are used widely in pharmaceuticals to control the release of drug. The approach of the present study was to evaluate the effect of type and ratio of polymer and plasticizers on the characters of desired sustained release pellets. It seems that Eudragit could be a suitable choice to prepare sustained release pellets containing Tramadol and with decreasing of drug taking intervals, the desired system

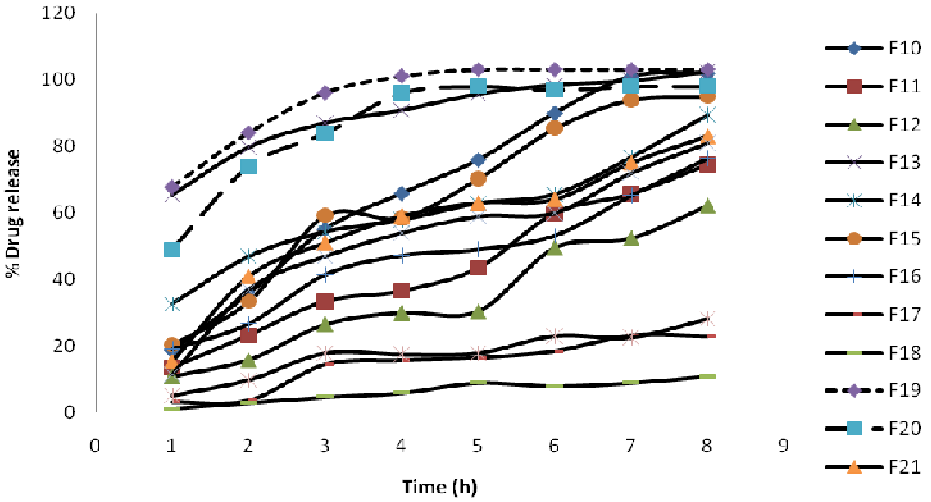

Figure 4. Drug release profile through formulation F10 - F21 in medium of acid and then PBS (pH: 6.8).

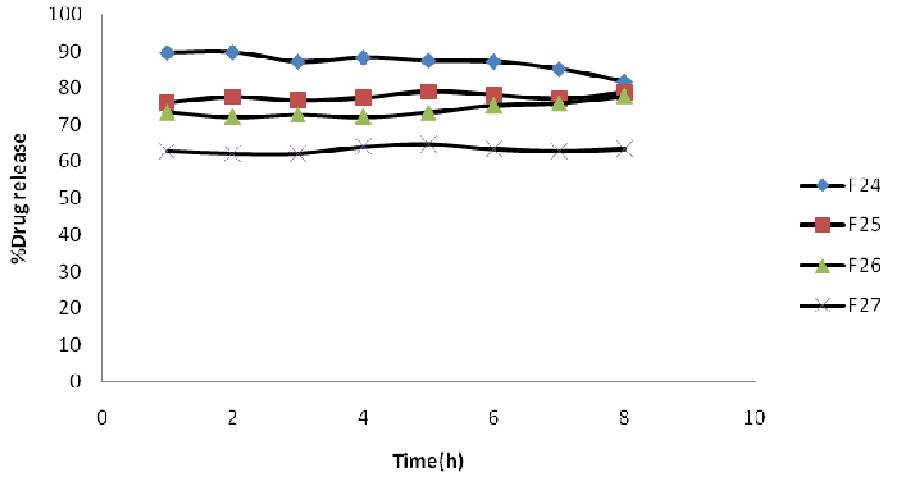

Figure 5. Drug release profile through formulation F24 - F27 in water medium.

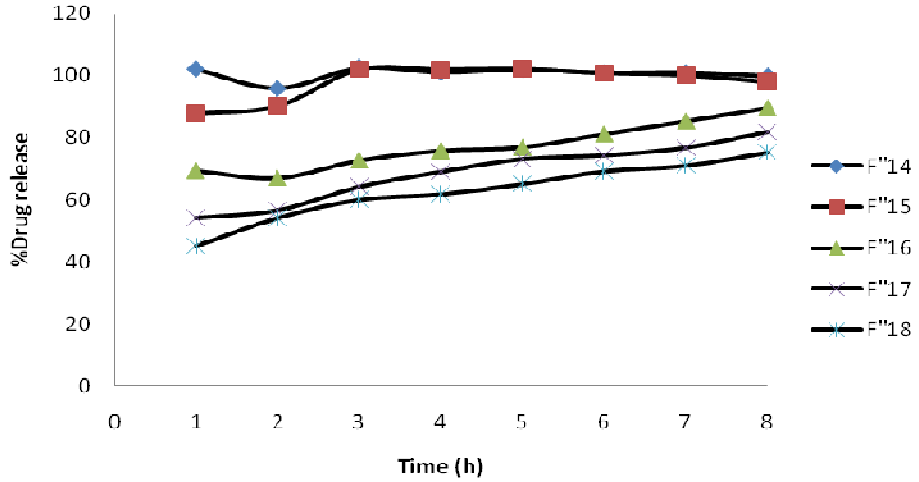

Figure 6. Drug release profile through formulation F"14 - F"18 in medium of acid and then PBS (pH: 6.8).

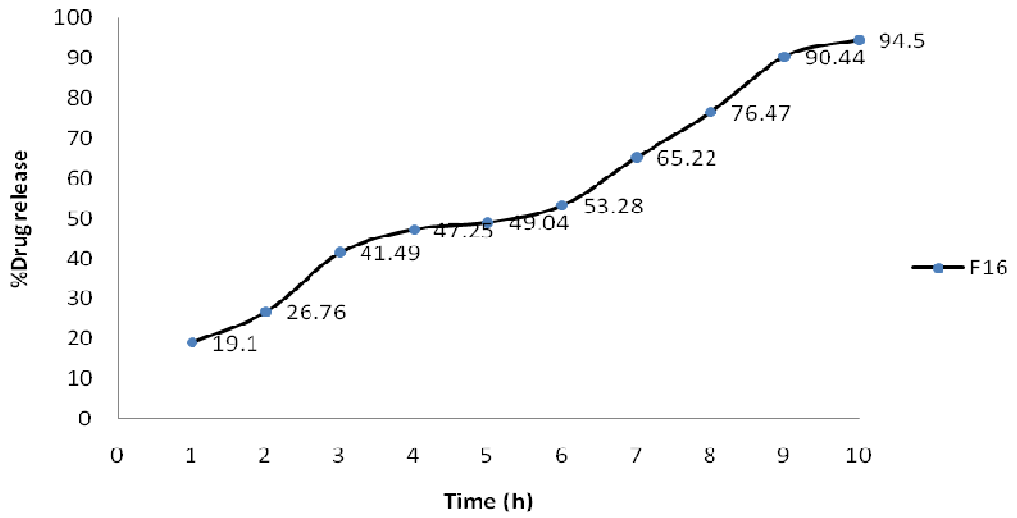

Figure 7. Drug release profile through formulation F16 in medium of acid and then PBS (pH: 6.8).

could increase compliance of patients and reduce doses and drug toxicity. Desired pellets could be filled in hard gelatin capsules to take by patients in the future after some modifications on drug loading efficiency and scale up procedure.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Research Vice Chancellor of Islamic Azad University of Medical Sciences for financial support of this project. Also, the authors thank Isfahan University of Medical Sciences. Authors would like to appreciate the support of Iranian Parenteral and Pharmaceutical Co (IPPC) and Jaber Ebne Hayyan Pharmaceutical Co. The technical assistance of Mr. Reza Jafarian was highly appreciated too. We also thank Professor Javad Farid, who supported us scientifically in this project.

REFERENCES

Adibkia Kh, Beirami MA, Barzegar-Jalali M, Mohammadi G, Shafiee Ardestani M (2012). Evaluation and optimization of factors affecting novel diclofenac sodium-eudragit RS100 nanoparticles. Afr. J. Pharm. Pharmacol. 6(12):941-947.

Bechegaard H, Nielson H (1978). Pellets: a general overview. Drug Dev. 4:53-67.

Bidah D, Vergnaud JM (1991). Dosage forms with a polymer matrix and a swelling Polymer. Int. J. Pharm. 77:81-87.

Dey NS, Majumdar S, Rao M (2008). Multiparticulate Drug Delivery Systems for Controlled Release. Trop. J. Pharm. Res. 7(3):1067-1075.

Esposito E, Roncarati R, Cortesi R, Cervellati F, Nastruzzi C (2005). Production of Eudragit microparticles by spray-drying technique: influence of experimental parameters on morphological and dimensional characteristics. Pharm. Dev. Technol. 5(2):267-78.

Garala KC, Shinder AJ, Shah PH (2009). Formulation and *in vitro* characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. Int. J. Pharm. Pharm. 1(1):108-121.

Ghaffari S, Sadri Alamdari N, Jafari Azar A, Dabir Siaghi AL, Kobarfard, F, Ghaffari S (2011). Preparation and Evaluation of Theophylline Sustained Release Microcapsules Using Coacervation. J. Disp. Sci. Technol. (In Press).

Ghai D, Bhaskaran S, Singh G, Sood M (2009). Extrusion spheronization as a drug delivery system: a technical note. Pharmainfo.net.

Golman K, Jalilpak RU (2008). The effect of the ratio of two acrylic polymers on the *in vitro* release kinetics of ketoprofen from pellets prepared by extrusion and spheronization technique. J. Pharm. Sci. 21(2):92-97.

Haritha NVV (2012). Multiple drug delivery system: Pelletization. AJPTR 2(1):81-87.

Hirjau M, Nicoara AC, Hirjau V, Lupuleasa D (2011). Pelletization techniques used in pharmaceutical fields. Farma 4(3,4):206-212.

Hu LD, Liu y, Tang x, Zhang Q (2006). Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. Eur. J. Pharm. Biopharm. 64:185-192.

Jan S, Khan GM, Khan H, Rehman AU, Khan KA, Shah SU, Shah KU, Badshah A, Hussain I (2012). Release pattern of three new polymers in Ketoprofen controlled-release tablets. Afr. J. Pharm. Pharmacol. 6(9):601-607.

Kibria G, Jalil R (2008). The effect of the ratio of two acrylic polymers on the in vitro release kinetics of ketoprofen from pellets prepared by extrusion and spheronisation technique. Pak. J. Pharm. Sci. 21(2):92-7.

Laila F, Chandran S (2006). Multiparticulate formulation approach to colon specific drug delivery: current perspectives. J. Pharm. Pharm. Sci. 9(3):327-338.

Liew CV, Wan LSC, Heng PWS (2000). Studies on spheronization processes by rotary and extrusion. Drug Dev. Ind. Pharm. 26:953-963.

Liu H, Shi Sh, Sun C, Zhao X, Shen Sh, He H (2012). Investigation of the pharmacokinetics of a novel sustained release metformin hydrochloride suspension with ion exchange resin as carriers in beagle dogs. Afr. J. Pharm. Pharmacol. 6(7):502-504.

Schaefer T, Kristensen HG (1993). Granulations in Encyclopedia of Pharmaceutical Technology. Marcel Dekker Inc., New York. Volume 7, pp. 121-160.

Shinde AJ, Garala KC, More HN (2008). Development and characterization of transdermal therapeutics system of tramadol hydrochloride. Asian J. Pharm. 2(4):265-269.

Trease GE (1964). Pharmacy in history. Tindal & Cox, Bailliere, London. pp. vii, 265, illus., 50*s*.

Yadav A, Jain DK (2011). Formulation development and

characterization of propranolol hydrochloride microballoons for gastroretentive floating drug delivery. Afr. J. Pharm. Pharmacol. 5(15):1801-1810.
Zhang H, Luo YH, Zhao XY, Chen Q, Luo M, Luo LY, Tian CC, Ge ZK, Zhang YJ (2012). Preparation of carteolol hydrochloride matrix sustained-release pellets and evaluation *in vitro/in vivo*. Afr. J. Pharm. Pharmacol. 6(11):829-833.