ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 6, Suppl 5, 2013

ISSN - 0974-2441

Research Article

EVALUATION OF NITROGLYCERIN SUSTAIN RELEASE FROM A MICRORESERVOIR TRANSDERMAL PATCH

JANFADA ALIREZA, TAVAKOLI JAVAD

Biomaterial Group, Biomedical Engineering Faculty, Science and Research Branch, Islamic Azad University, Tehran, Iran,
Email: drjavadtavakoli@yahoo.com

Received: 4 September 2013, Revised and Accepted: 30 October 2013

ABSTRACT

Achieving a systemic effect of a drug by delivery through skin is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. The development of transdermal drug delivery systems is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of a drug molecule to the demonstration of sufficient drug flux in an ex vivo and/or in vivo model. The present study was undertaken to investigate the effect of formulation parameters on nitroglycerin release profile from a micro-reservoir transdermal silicon patch. Initial nitroglycerin concentration, amount of crosslinking agent and co-solvent (PEG400) whose effect on release profile was studied were the formulation parameters. Also physicochemical evaluations (patch thickness, weight uniformity, flatness, drug content and content uniformity) were tested. Also, release profile and rate were measured using a designed diffusion cell with and without skin and the results were compared.

Keywords: Transdermal drug delivery, nitroglycerin, silicon patch, sustain release, micro-reservoir

INTRODUCTION

Nitroglycerin is used extensively for the treatment of angina pectoris. In the conventional oral dosage form, nitroglycerin is metabolized to dinitrate compounds in the liver which have only 5% of the activity of nitroglycerin, making the oral route not very effective or causes side effects[1].With the use of transdermal delivery systems, nitroglycerin concentration in the systemic circulation can be controlled at the therapeutic level for as long as few days[2,3]. Transdermal nitroglycerin patches were originally introduced as a sustained-action nitroglycerin delivery system when pharmacokinetic studies showed that this formulation produced steady-state blood concentrations when affixed to skin[4-6]. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. Transdermal drug delivery systems are broadly classified into three types[7].

In reservoir system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane, which is micro-porous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied[8].

Matrix types divided into two major parts. In drug-in-adhesive system the drug reservoir is formed by dispersing in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) onto an impervious backing layer. On top of the reservoir, layers of un-medicated adhesive polymer are applied[9]. In Matrix-dispersion system,the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim[10].

The Micro-reservoir system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of un-leachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ[11].

The objective of this research was to investigate the effect of formulation parameters on nitroglycerin release from a micro-reservoir transdermal patch.

NITROGLYCERIN RELEASE THROUGH SILICON MATRIX

In silicon matrix diffusion-controlled transdermal delivery systems, the drug reservoir is formed by homogeneously dispersing the drug solids in a lipophilic silicon matrix and is molded into medicated disks with defined surface area and thickness. The rate of release from silicon matrix drug dispersion-type could be calculated as Eq. 1:

$$\frac{dQ}{dt} = \sqrt{\frac{D.C.S}{2t}} \qquad (1)$$

Where, C is drug initial concentration dispersed in silicon matrix, S and D, are solubility and diffusivity of nitroglycerin in silicon matrix, respectively. In matrix drug delivery system only drug dissolved in polymer matrix can diffuse in which drug solubility in the matrix is estimated to be equal to drug concentration in reservoir compartment. In another similar type, which is fabricated by directly dispersingdrug in a pressure-sensitive adhesive and solvent casting the governing equation is mentioned in Eq. 2. It should be noticed that skin is the only controlling site for drug delivery if a layer of non-medicated rate controlled adhesive polymer of constant thickness doesn't applied. Diffusivity of drug depends on matrix thickness and its physicochemical characteristics.

$$\frac{dQ}{dt} = \frac{K.D.C}{h} \qquad (2)$$

Where K is partition coefficient for interfacial partitioning of the drug form the reservoir layer to the adhesive layer, D is diffusion coefficient, C is drug concentration in reservoir compartment and h is thickness of adhesive layer.

In micro-reservoir dissolution-controlled transdermal delivery system, a hybrid of reservoir and matrix dispersion-type drug delivery systems which contains dug reservoir formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer, then homogeneously dispersing the drug suspension with controlled aqueous solubility in a lipophilic polymer by high shear mechanical force to form thousands of un-leachable microscopic drug reservoirs. This thermodynamically unstable system is quickly stabilized by immediately cross-linking the silicon chains in situ, which produces a medicated polymer disk with a constant surface area and a fixed thickness. In this state Eq.3 is introduced as governing equation of drug release rate.

$$\frac{dC_d}{dt} = D_d \frac{d^2C_d}{dx^2} + \frac{C_{NR} - C_d}{\frac{r_D - r_i}{4\pi r_i r_D D_d}} . C_b \qquad (3)$$

Where Eq.3's variables are defined as: C_b= number of microcapsules /cm^3, C_d= concentration of drug, D_d= diffusivity of drug in matrix, C_{NR}= concentration of drug in the core of microcapsule, r_D= radius of microcapsule outside and r_I= radius of microcapsule inside

MATERIALS AND METHODS

Materials

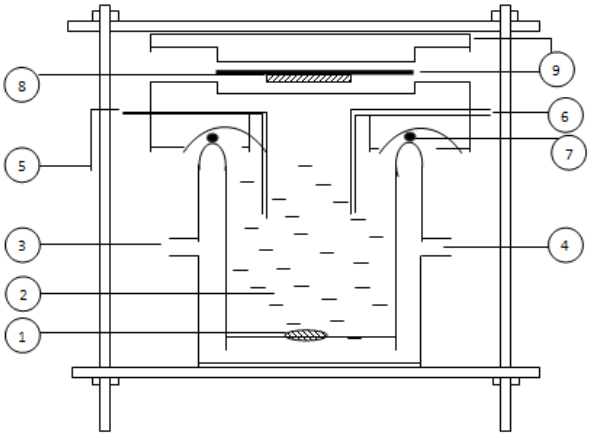
Room temperature vulcanization silicon rubber (Silastic 3481) was used as a hydrophobic phase. PEG400 (Sigma Aldrich, Germany) was used as the co-solvent for the dispersed aqueous phase. Nitroglycerin (SOHA pharmaceutics), as a 10% solid solution in lactose with 150 mesh size was used. All chemicals were used without further purification.

Patch preparation

A typical procedure for preparation of nitroglycerin transdermal patch was as follows. To prepare the dispersed phase 6 g of 10% nitroglycerin in lactose was mixed with 3.6 g distilled water and 0.4 g PEG400 until a creamy paste was obtained. The percentage of nitroglycerin in the aqueous phase was 6%. The aqueous phase was dispersed in the RTV silicon matrix using a high speed blender for 5 min at ambient conditions. Next the crosslinking agent was added and mixing was continued for additional 3 min. The mixture was poured into 8×8 cm Teflon coated aluminum mold, with thickness ranging from 1 to 3 mm, and allowed to cure for 12 h at 40°C. After curing the surface of the molded patches where coated with a layer of RTV silicon rubber containing the curing agent without the dispersed phase to seal the surface. Patches with surface area ranging from 12 to 20 cm^2 were punched from the cured film and stored in a closed container. In order to evaluate formulation parameters on nitroglycerin release, amount of PEG400, diluted nitroglycerin in lactose and crosslinking agent varied for each individual patches.

Release test

A patch diffusion cell was constructed. A schematic diagram of the diffusion cell is shown in Fig 1. The diffusion cell consisted of a 400 ml receiver compartment, completely surrounded by a glass water jacket containing inlet and outlet ports for connection to a water bath. The receiver solution was stirred with a Teflon coated magnetic stir bar. The receiver compartment was covered by a Teflon template which had a circular aperture in the center, with diameter ranging from 3 to 5 cm. Two 16 gauge needles in the template served as sampling ports. The outer assembly, made of Plexiglas, was used with a stainless steel clamping ring to clamp the cell together. An o-ring between the template and the glass cell ensured a leak-proof seal. A polyester sheet was adhered to the template and the patch was attached to the sheet with the delivery surface in direct contact with the receiver fluid. The agitator speed was set at 20 rpm. All release studies were performed with 1) the patch and 2) the combination of patch and goat skin in direct contact with de-ionized water.The goat hairless skin was prepared by veterinary Faculty of Tehran University.



Row	Part No.	Description
1	1	Stir bar
2	2	Receiver compartment
3	3	Outlet port
4	4	Inlet port
5	5	Sampling port
6	6	Sampling port
7	7	o-ring
8	8	Patch
9	9	Polyester sheet

FIG.1: Schematic diagram of the patch diffusion cell

Release measurement:

For release measurement, the receiver compartment was filled with de-ionized water and its temperature was kept at 37 °C. The amount of nitroglycerin release was measured by taking 2 ml aliquots from the receiver solution, replacing with deionized water and measuring the concentration with HPLC. The HPLC column was filled with C-14 and the mobile phase consisted of equal volume of methanol and water with a velocity of 1.2 ml/min. The wavelength of UV detector was set at 220 nm.

Physico-chemical evaluation:

Patch thickness, weight uniformity, flatness, drug content and content uniformity were tested. In drug content determination,accurately weighed portion of patch was dissolved in 100 ml of suitable solvent (equal mixture of methanol and deionized water) in which drug was soluble and then the solution was shaken continuously for 24 h in shaker incubator. Then the whole solution was sonicated. After sonication and subsequent filtration, drug in solution was estimated by a spectrophotometer at 220 nm with appropriate dilution.In content uniformity test 10 patches were selected and content was determined for individual patches. The procedure was the same for all samples.

drug content determination:

For flatness evaluation, one narrow piece was cut from the center and two from each side of 3 patch groups. Each group consisted of patches with different amount of crosslinking agents with different thicknesses. The length of each strip was measured and variation in length was measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.Transdermal patch should have a smooth surface and should not constrict with time. Weight variation was studied through individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not

deviate significantly from the average weight. The thickness of transdermal patch was determined by a micrometer, traveling at different points of the patch.

RESULTS AND DISCUSSIONS

Conducted tests for flatness evaluation showed more than 98% flatness for each three specimens with different thickness (Table 1). Constriction percentage was calculated by Eq.4:

$$constriction\,(\%) = \frac{L_i - L_f}{L_i} \times 100 \qquad (4)$$

Where L_i and L_f are initial and final specimen's length, respectively. It was also evaluated that thickness variation had very negligible effect on patch's flatness however increasing crosslinking agent caused more constriction. This could be concerned as the effect of crosslinking agent on rubber elasticity of silicon network. Increasing vulcanization agent on patch formulation reduced network elasticity.

Table 1: Flatness test for transdermal patches with different formulation

row	Patch Specification	Thickness (mm)	Crosslinking agent (%)	Flatness (%)
		1	1	99.6
1	Group A	1	3	99
		1	5	98.1
		1	1	99.6
2	Group 2	3	1	99.6
		5	1	99.5

In weight uniformity test all specimens were passed the test criteria. The individual weight did not deviate significantly from the average weight of the samples. Thickness uniformity for 3 patches with different thicknesses (1,3 and 5 mm) which conducted for 10 points with 3 individual measurements in each area showed acceptable uniformity for each specimen. Not more than 1% difference was shown not only in thickness differences before and after crosslinking process but also in different regions of measurement. All data were compared as an average.

Fig 2 shows drug content evaluation for patches containing 20% active agent. 10 patches were examined with described test method. 9 out of 10 patches had content more than 85% of the specified value and one had contentnot less than 75% to 100% of the specified value, then transdermal patches pass the test ofcontent uniformity. For each patches drug content was also satisfactory as more than 99% of drug content left the patch within 24 hours under continuous stirring.

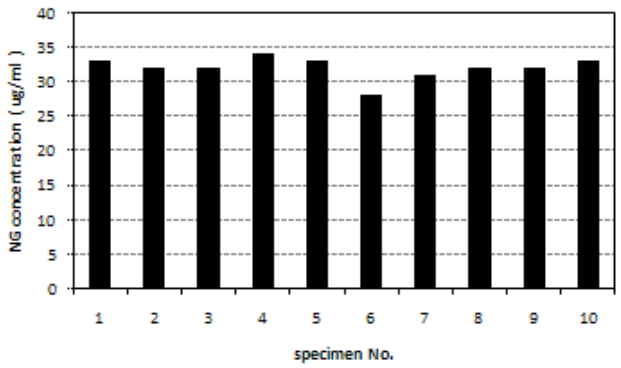


FIG.2: Drug content and drug content uniformity results

In general, variation of nitroglycerin concentration through disperses and continuous phases of micro-reservoir transdermal delivery system could be shown as Fig 3, schematically. According to that diffusion of nitroglycerin from lactose phase to aqueous phase occurs by concentration gradient and diffusion between aqueous phase and silicon matrix happens in interface of continuous-disperse phase whose partition coefficient and nitroglycerin solubility controls diffusion rate. Nitroglycerin molecular diffusion in silicon matrix could be described by uniform distribution of its concentration whose positive outward resultant facilitates drug release into the surface of the patch. In the interface of patch (continuous phase) and release media, hydrodynamic diffusional layer in the surface and skin structure is the most controlling parameter of nitroglycerin transdermal delivery system.

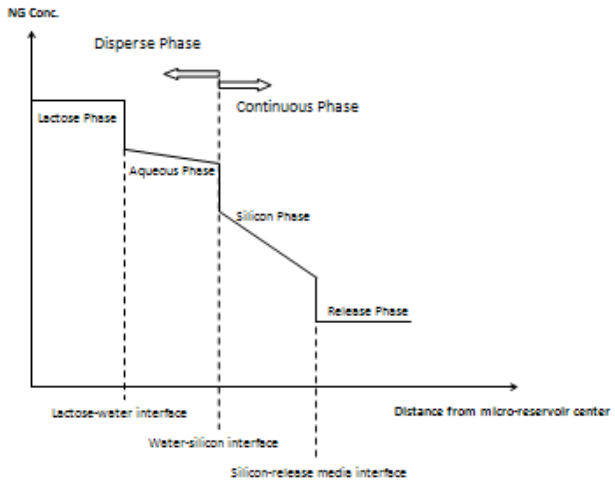


FIG.3: Variation of nitroglycerin concentration with distance from micro-reservoir to release media.

So by considering all mentioned parameters' contribution in nitroglycerin transdermal delivery, its release rate could be calculated by Eq. 5:

$$J = \frac{k_1 k_2 S_w}{\frac{k_2 d_s}{D_s A_w} + \frac{k_1 k_2 d_w}{D_w A_0}} \qquad (5)$$

Where k_1 and k_2 are partition coefficient between aqueous phase–silicon matrix and silicon matrix–release media, respectively. S_w and C_b are solubility and concentration of nitroglycerin in release media. d_w and d_s are thickness of aqueous and silicon phase. A_w and A_0 considered as micro-reservoir and patch area, respectively and D_w and D_s are nitroglycerin diffusion coefficient in aqueous and silicon phase. Considering nitroglycerin initial concentration in formulation and its solubility coefficient in water (5.5×10^{-3}) less than 15 ml of water is required for saturation condition achievement. Therefore release media volume (400 ml) is large enough to consider C_b equal to zero. In other hand as $k_2 >> k_1$, simplified form of Eq. 5 could be considered as Eq. 6:

$$J = \frac{k_1 S_w D_s A_w}{d_s} \qquad (6)$$

It means in our study, release rate significantly controlled by partition coefficient between aqueous and silicon phase, solubility of nitroglycerin in aqueous phase and diffusion coefficient of nitroglycerin in silicon phase.

Fig 4 shows the release rate of nitroglycerin as a function of time for a patch with diameter of 4 cm, thickness of 1 mm and with 1.2% active agent. The release rate was higher than the therapeutic level required for nitroglycerin. More ever, only a slight decrease in release rate was observed over time which indicated it has the characteristic of a reservoir device. In presence of goat skin in release test, release rate of nitroglycerin shifted to therapeutic level by 35% nitroglycerin concentration decreasing. Also a little negative slope variation in trend line was seen which may referred to release moderating property of skin by including its partition coefficient into account.

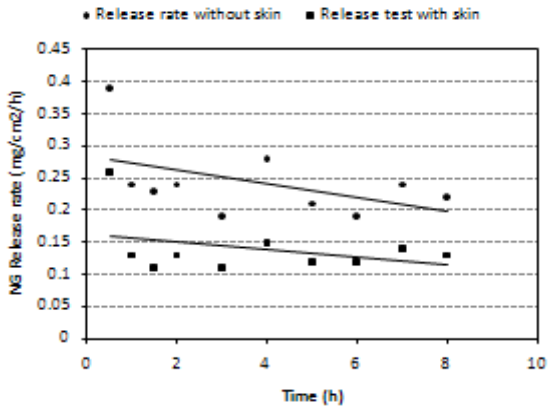


FIG.4: Release rate of nitroglycerin versus time for two different test conditions.

The effect of nitroglycerin concentration was investigated by changing the concentration of lactose and nitroglycerin mixture in dispersed phase from 20 to 30 wt% corresponding to 12 and 18 wt% concentration of nitroglycerin in the patch. The results are shown in Fig. 5. When the concentration of nitroglycerin was changed from 1.2 to 1.8%, the release rate changed from 3.0 to 6.5 µg/ml/h and the total amount released after 9 h was 30 and 72 µg/ml, respectively. These results indicated that release of nitroglycerin was strongly affected by the concentration of nitroglycerin in the patch, as predicted by Higuchi model. According to this model release study of water-soluble drug and low soluble drugs incorporated in the solid/semisolid matrixes performed by Eq.7:

$$Q = \sqrt{D(2C - C_s)C_s t} = K_H\sqrt{t} \qquad (7)$$

Where Q is the amount of the drug released in time t per unit area, C is the initial drug concentration, C_s is the drug solubility in the matrix media, D is the infusibility of the drug molecules in the matrix substance and K_H is the Higuchi dissolution constant. Equation (7) could be used to determine the release rate of different formulation which obtained by plotting the graph between amounts of drug release versus $(t)^{1/2}$. In our study Higuchi dissolution constant was equal to 1.77 and 1.46 for 30% and 20% initial drug concentration, respectively. Also it could be seen that concentration of released nitroglycerin reached a plateau level in 20% active agent formulation during 9 hours meanwhile 30% active agent formula may be able to continue drug release for a few more hours as no constant concentration profile in release media was seen. It means release time was directly affected by initial nitroglycerin concentration.

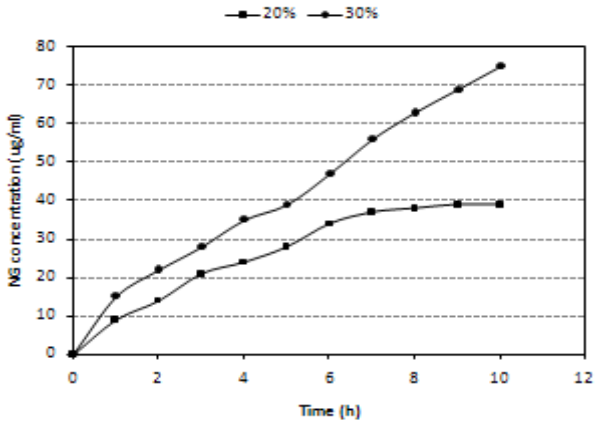


FIG.5: Effect of nitroglycerin concentration on the amount of nitroglycerin release versus time

Fig 6 shows the effect of PEG400 concentration in the dispersed phase was doubled from 4 to 8 wt%, the amount released after 9 h increased from 77 to 88 µg/ml, corresponding to an increase of 13%. Therefore, the concentration of PEG400 had a slight effect on nitroglycerin release which indicated that the release process was only partially controlled by the partition coefficient of nitroglycerin between the lactose and water phases. It is well known that polymer is an integral and foremost important component of transdermal drug delivery systems. Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device. As no single material may have all proper properties, co-solvents such as PEG 400 could be added to increase drug solubility. Also using PEG 400 in continuous phase as plasticizer shows better enhancing effects.

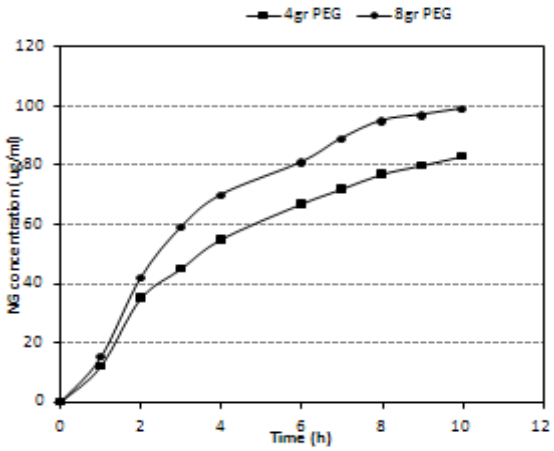


FIG.6: Effect of PEG400 concentration on the amount of nitroglycerin release as a function of time.

As it is proved before, release rate significantly was affected by diffusion coefficient of nitroglycerin in silicon phase. So increasing of crosslinking agent in formulation whose direct effect on silicon network is more polymeric chain integrity and less polymeric chain mobility decreased nitroglycerin release through patches. Fig 7 shows the effect of crosslinking agent variation on nitroglycerin release from transdermal delivery system.

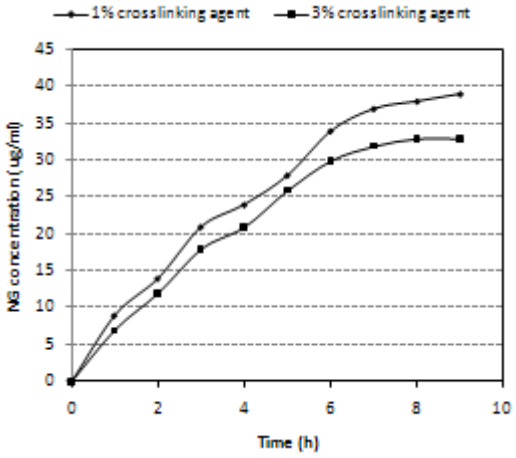


FIG.7: Effect of crosslinking agent concentration on nitroglycerin release

CONCLUSION

The release of Nitroglycerin was strongly affected by its total concentration in the patch, as predicted by Higuchi model. The concentration of PEG400 in the dispersed phase had a slight effect on Nitroglycerin release which indicated the release process was

partially controlled by the partition of Nitroglycerin between lactose and water phase. Increasing of crosslinking agent in formulation whose direct effect on silicon network is more polymeric chain integrity and less polymeric chain mobility decreased nitroglycerin release through patches.

ACKNOWLEDGMENT

We wish to thank SOHA Pharmaceutical Complex a subsidiary of HelalAhmar Iran for gifting Nitroglycerin.

REFERENCES

1. Glantz L,Godovic G, Lekar M,Kramer M,Eidelman LA Efficacy of transdermal nitroglycerin combined with etodolac for the treatment of chronic post-thoracotomy Pain: an open-label prospective clinical trial, Journal of Pain and Symptom Management, Vol.27, No.3,2004, 277-281.
2. Dinh SM, Comfort AN, Shevchuk I, Berner B Temporally controlled transdermal systems: biphasic transdermal delivery of nitroglycerin, Journal of Membrane Science, Vol.89, 1994, 245-255.
3. Elgohary MM, Transdermal nitroglycerine potentiates the analgesic effect of patient controlled epidural analgesia after lower abdominal surgery, Egyptian Journal of Anesthesia, Vol.27, 2011, 19-24.
4. Agvald P, Hammar L, Gustafsson LE Nitroglycerin-patch induced tolerance is associated with reduced ability of nitroglycerin to increase exhaled nitric oxide, Vascular Pharmacology, Vol.43, 2005, 449 – 457.
5. PervizKazemi A, Zand F, Sedaghat M Blood–sparing efficiency of transdermal nitroglycerine during open fixation of femur shaft fractures: a randomized, double-blind study, Journal of Clinical Anesthesia, Vol.18, 2006, 495–498.
6. Ashok kumar J, pullakandam N, Pabu SL, Gopal V Transdermal drug delivery, system: an overview, International Journal of Pharmaceutical Sciences Review and Research, Vol.3,2010, 49-54.
7. Heather Benson AE Transdermal drug delivery: penetration enhancement techniques, Current Drug Delivery, Vol. 2, 2005, 23-33.
8. Selim Reza MD, Abdul Quadir M, Haider SS Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery, J Pharm PharmaceutSci, Vol.6, 2008, 282-291.
9. ThosarMilind M, Pancholil SS Review on penetration enhancement techniques in transdermal delivery system, American journal of pharmatec research, Vol. 2, 2012, 2249-3387
10. Kumar GI, ChokshiMaulesh M Transdermal drug delivery system: an overview, Asian Journal of Pharmaceutical Sciences and Clinical Research, Vol. 1, Issue 1, 2011, 25-43.