www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(7): 638-648

www.thepharmajournal.com
Received: 15-05-2018
Accepted: 17-06-2018

Kota Raveendhra
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Sasikanth Kothamasu
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Suryakanta Swain
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Manohar Babu S
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Correspondence
Kota Raveendhra
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Formulation and evaluation of controlled release topical gel of baclofen

Kota Raveendhra, Sasikanth Kothamasu, Suryakanta Swain and Manohar Babu S

Abstract
The objective of present study was to develop controlled release topical gel of baclofen 0.5%w/w using hydrophilic polymers such as Carbopol, Xanthum, Carrageenan, Sodium alginate etc as gelling agents. Results revealed that prepared gel systems showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F13 formulation was found to be stable as there was no drastic change in the physicochemical properties. Thus conclusion can be made that stable topical hydrogels of baclofen has been developed. F13, F7 formulations showed highest cumulative percentage drug release of 98.98%, 96.46% were obtained during *in vitro* drug release studies after 24 hrs and F18 formulation showed 99.74% after 22 hr. The release of baclofen appears to be dependent on concentration of polymer. High viscous polymeric network showed showed best release. High viscosity of the gel system acts as a barrier in between the drug and site of absorption (skin). During the *in vitro* drug permeation study conducted on F13, F17 and F18 formulation showed cumulative amount of drug permeation of 662.87, 659.19, 661.20 µg/cm^{2}/hr respectively. The *ex vivo* skin permeation studies were conducted on F13, F17and F18 formulations, the F13 formulation exhibited high (662.87) cumulative amount of drug permeation through abdominal rat skin when compare with other formulations i.e. F17(649.47), F18(659.96). The F13 formulation showed flux of 4.2743 µg/cm^{2}/hr with permeability coefficient of Kp 1.4247. Based upon the *in vitro* dissolution data and *in vitro* drug permeation data the F13, F17 and F18 formulations showed similar drug release but upon *ex vivo* permeation studies it was found that F13 formulation showed superior drug release, therefore F13 formulation was concluded as optimized formulation.

Keywords: baclofen, topical gel, carbopol, xanthum, carrageenan, sodium alginate, *in vitro* drug release studies, e*ex vivo* permeation studies

1. Introduction
Topical drug delivery systems
Topical drug delivery systems are gaining increase in popularity and several drugs have been successfully delivered by this route for both local and systemic action. In recent years, most of non-steroidal anti-inflammatory drugs (NSAID's) have been designed to deliver the drug in the form of topical gels, to avoid gastrointestinal irritation, to overcome "first pass" effect and to maximize the drug concentration at the sight of action. Gels have better potential as a vehicle to administered drug topically in comparison to ointment, because they are non-sticky, requires low energy during the formulation, are stable and have aesthetic value. Gels are transparent to opaque semi solids containing a high ratio of solvent to gelling agent. Gels tend to be smooth, elegant, non-greasy and produce non-greasy effect and utilize better drug release when compared to semi solid formulations. Drug delivery through the skin has been a promising concept for a long time because skin is easy to access, has a large surface area with vast exposure to the circulatory and lymphatic networks and the route is noninvasive. Transdermal delivery is of great importance for drugs that may cause systemic side effects such as non-steroidal anti-inflammatory drugs [1, 2].

Topical drug delivery systems are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. They are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through skin at a desired rate to systemic circulation (monk house, 1988). In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered [3].

A gel (from the latingelu-freezing, cold, ice or *gelatus*-frozen, immobile) is a solid, *jelly-like material* that can have properties ranging from soft and weak to hard and tough. Gels are defined as a substantially dilute *cross linked* system, which exhibits no flow when in the steady-state [1]. By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid. It is the crosslinking within the fluid that give a gel its structure (hardness) and contribute to the adhesive stick tack, in this way gels are a dispersion of molecules of a liquid within a solid in which the solid is the continuous phase and the liquid is the discontinuous phase. Topical gel formulations provide a suitable delivery system for drugs because as they are less greasy and can be easily removed from the skin. Percutaneous absorption of drugs from topical formulations involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed. In order to enhance drug release and skin permeation, methods such as the selection of a suitable vehicle, co-administration of a chemical enhancer have been studied. Gel base formulation makes the drug molecules more easily removable from the system than cream and ointment. Gels for dermatological use have several favorable. Properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients and water-soluble or miscible [4, 5].

Baclofen (4-amino-3-(4-chlorophenyl) butanoic acid) inhibitor used in a variety of inflammatory, pain. Baclofen is an effective as classical Nonsteroidal anti-inflammatory drug (NSAID) for the relief of a wide variety of pain and inflammatory conditions, but it is better tolerated than other (NSAIDs). After oral administration the drug is rapidly and extensively absorbed. It is rapidly distributed, and eliminated with a terminal half-life of about 2.5-4hr. approximately 85% of the dose is excreted as unchanged drug in urine and remainder is excreted in faeces. Baclofen is mainly cleared from the body by metabolic transformation in the liver primarily by deamination [6].

2. Materials and methods

2.1. Materials Used

Baclofen, Carbopol 71 G, Carbopol 934, Carragenan, Disodium hydrogen orthophosphate, D-Maleic acid, Na CMC, Oleic acid, Transcutol, Triethanolamine.

2.2. Experimental Methods Used

Solubility measurement

1gm of substance was made to dissolve in various solvents individually and the solvent was added till the drug completely gets dissolved. The amount of solvent consumed is reported as solubility [7].

Partition coefficient

The partition coefficient of the drug was determined by shaking equal volumes of organic phase (n-heptane) and the aqueous phase in a separating funnel. A drug solution of 1mg/ml was prepared with distilled water and 50ml of this solution was taken in a separating funnel and shaken with an equal volume of n-heptane for 10 minutes and allowed to stand for 24 hrs with intermittent shaking. Then, the concentration of baclofen in the aqueous phase was determined using a UV-Visible spectrophotometer at 220nm to get the partition coefficient value. The partition coefficient (log p) was calculated using the following equation [8].

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}} \quad (6)$$

Melting point determination

Melting point of drug was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in melting point apparatus and temp at which the drug melts was noted [9].

Permeability studies through rat abdominal skin

Preparation of the skin barrier

Albino rats weighing 150-200gms were sacrificed using anesthetic ether. The hair of test animals were carefully trimmed short (<2mm) with a pair of scissors and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique, which involved soaking the entire abdominal skin in water at 60^{o}C for 45seconds, followed by careful removal of the epidermis. The epidermis was washed with water and used for *in vitro* skin permeability studies [10].

***In vitro* drug permeation studies through rat abdominal skin:**

The aim of this study was to determine the permeability of skin to baclofen.

Procedure

The skin was carefully mounted between the two compartments of a Franz diffusion cell with internal diameter is 2.4 cm (4.52cm^2 area) and with a receptor compartment volume of 25ml. The barrier was mounted between the donor and receptor compartments in a way that, the dermal side of the skin was facing towards receptor compartment. A 1mg/ml drug suspension was prepared in phosphate buffer pH 6.8 and sonicated to ensure to uniform drug distribution. 1ml of the above suspension was taken in the donor compartment. The receptor compartment fluid consists of 25 ml of phosphate buffer pH 6.8. The entire setup was placed over magnetic stirrer and temperature was maintained at about 37± 0.5^{0}C. The samples were collected at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hrs and analyzed sprctrophotometriclly at 220nm [12-15].

Compatibility studies of drug and polymers

In the preparation of gel, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between baclofen and the selected polymers. The pure drug and drug with excipients were scanned separately.

Preparation of topical gel of Baclofen

Topical gel of baclofen were prepared as hydrogel by using hydrophilic polymers such as Carbopol 934, Carbopol 71G, Xanthum, PEO WSR303, Na CMC, Natrasol, Keltone, Carragennan. Initially accurately weighed amount of drug (250mg) was dissolved in 15ml distilled water in acidic condition. Methyl paraben 50mg (optimized preservative) was dissolved in 30ml of distilled water by heating at 50^{0}C then cooled to room temperature and required amount of polymer was dissolved in it. To this drug solution which was

previously dissolved in acidic water was added. The total content was stirred by using homogenizer, care was taken to prevent the formation of lumps finally 0.7ml of Triethanolamine was added to neutralize the gel to pH 6.2 to 7.2, Triethanolamine also acts as viscosity increasing agent then the weight was adjusted to 50 gr with the addition of water. The prepared gel was set aside for 24 hours for polymer stabilization and to exclude any entrapped air, vacuum was applied if necessary and was then transferred into a previously cleaned collapsable tube, then packed and stored for further evaluation [16-18].

Evaluation of topical gel formulation [18-20]

Physical evaluation

All the formulations of baclofen sodium were evaluated for organoleptic characteristics, occlusiveness and washability.

Appearance

Colour is important for patient compliance. The prepared gels were inspected visually for clarity, colour and presence of any particle.

Measurement of pH

The pHs of the formulated gels were determined using digital pH meter. The electrode was immersed in the gel and readings were recorded from pH meter.

Spreadability

A sample of 0.1 g of each formula was pressed between two slides and left for about 5 minutes where no more spreading was expected. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are average of three determinations.

Homogeneity and grittiness

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. Also, the homogeneity can be detected when a small quantity of the gel is rubbed on the skin of the back of the hand. The grittiness of prepared gel is also observed in the same manner.

Extrudability study

The extrudability of gel formulations were determined by filling gel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel.

Drug content

A specific quantity (100mg) of developed gels were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 220.0nm using phosphate buffer (pH 6.8) as blank. Drug content was calculated by the following formula

Drug content = Absorbance /slope × Dilution factor ×100× 100×1÷ 100

Stability studies

Optimized formulated gels were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

***In vitro* release study**

USP paddle method

The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The dissolution studies of patches are crucial because one needs to maintain the drug concentration on the surface of the SC consistently and keep it substantially higher than the drug concentration in the body, to achieve a constant rate of drug permeation.

The drug release was determined using USP type II dissolution apparatus thermo stated at 37 ± 0.5 ^{0}C and stirred at a rate of 25 rpm. Each gel formulation was kept in a dialysis membrane of 50 kilo Daltons. The other side of the dialysis membrane was covered to prevent drug release from that side, and the poutch was prepared as the effective surface area was equal to about 4.52 cm^2, the remaining area was covered with cellophane tape.

Each pouch was fixed on a glass slide with the help of adhesive, so that the drug could be released from upper face. The slide was immersed in the vessel containing 500ml of phosphate buffer pH 6.8. Aliquots of 5ml of samples were withdrawn at different time intervals and then analyzed using a UV Spectrophotometer at 220 nm against blank.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100 \quad (14)$$

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released

***Ex vivo* skin permeation study of topical gel of baclofen**

Ex vivo permeation of topical gel of baclofen through rat abdominal skin was studied. Rat skin was obtained and epidermis was isolated. The rat skin was mounted between the compartments of the diffusion cell with SC facing the donor compartment. The SC side of the skin was kept in intimate contact with the gel system under test. The receptor compartment is filled with 25ml of phosphate buffer pH 6.8, stirred at 250 rpm on a magnetic stirrer; the whole assembly was kept at 37 ± 0.5 ^{0}C. Samples of 3 ml were withdrawn from the receiver compartment at different time intervals, the volume was replenished with an equal volume of phosphate buffer pH 6.8. The absorbance was measured at 220nm in UV- visible spectrophotometer against blank.

3. Results

Table 1: Formulation design of topical gel of baclofen containing drug: polymer in 1:2 ratio

Formulation Code	Ingredients (mgs)								
	Drug	Carbopol 934	Xanthum	NaCMC	Natrasol	Keltone	Carragenan	PEO	Carbopol 71G
F1	250	500	-	-	-	-	-	-	-
F2	250	-	500	-	-	-	-	-	-
F3	250	-	-	500	-	-	-	-	-
F4	250	-	-	-	500	-	-	-	-
F5	250	-	-	-	-	500	-	-	-
F6	250	-	-	-	-	-	500	-	-
F7	250	-	-	-	-	-	-	500	-
F8	250	-	-	-	-	-	-	-	500
F9	250	250	250	-	-	-	-	-	-
F10	250	-	250	-	250	-	-	-	-
F11	250	-	250	-	-	250	-	-	-
F12	250	-	250	-	-	-	250	-	-

Table2: Formulation design of topical gel of baclofen containing drug: polymer in 1:4 and 1:6 ratio

Formulation code	Ingredients (mgs)								
	Drug	Carbopol 934	Xanthum	NaCMC	Natrasol	Keltone	Carragenan	PEO	Carbopol 71G
F13	250	1000	-	-	-	-	-	-	-
F14	250	-	-	-	-	-	-	-	1000
F15	250	500	-	-	-	-	-	-	500
F16	250	-	1000	-	-	-	-	-	-
F17	250	1500	-	-	-	-	-	-	-
F18	250	-	1500	-	-	-	-	-	-

Table 3: Solubility measurement of baclofen

S.no	Vehicle	Amount of vehicle (ml)	Amount of drug(mg)
1	Distilled water	500	1000
2	Distilled water at 60ºC	250	1000
3	0.1N HCl	41	1000
4	Transcutol-P	500	1000
5	Olive oil	1500	1000
6	PEG 400	1000	1000
7	Propylene glycol	1500	1000
8	Aloe juice	333	1000
9	Emu oil	1000	1000
10	Span 60	2000	1000

Table 4: *In vitro* drug permeation of baclofen through rat abdominal skin

Time (hr)	Cumulative amount permeated (µg/cm^2)
0	0
0.5	66.99±1.03
1	67.07±1.09
2	74.01±1.12
4	77.86±1,31
6	112.56±1.54
8	177.32±1.76
10	219.73±1.21

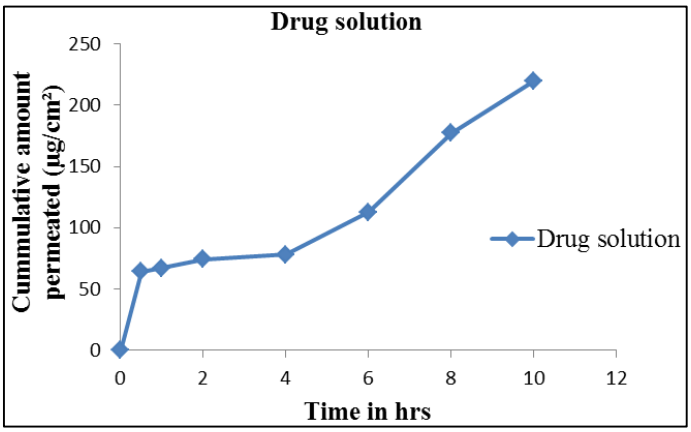

Fig 1: *In vitro* drug permeation of baclofen through rat abdominal skin

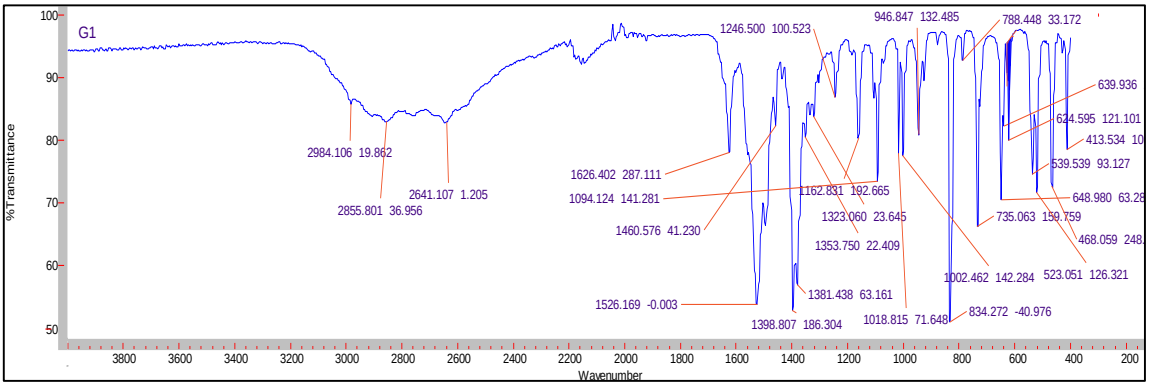

Fig 2: FT-IR Spectra of Baclofen

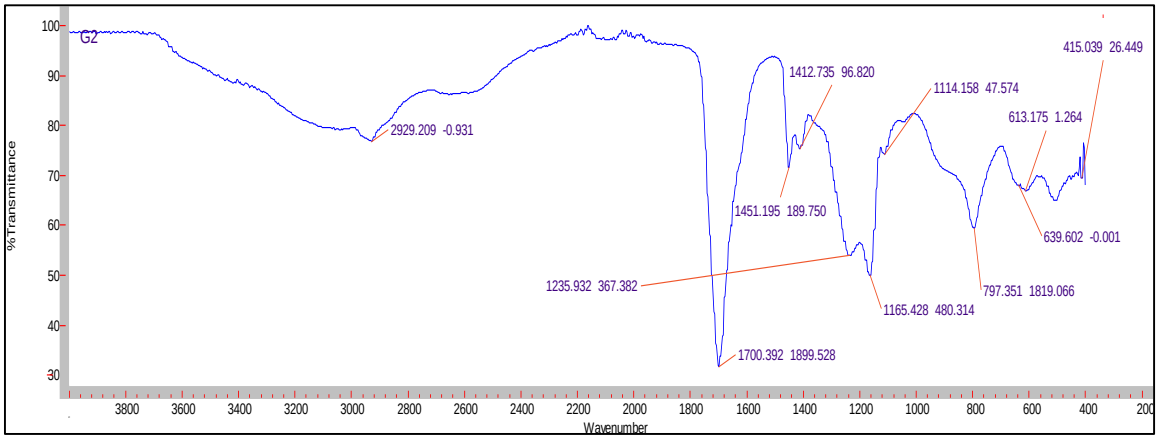

Fig 3: FT-IR Spectra of Carbopol 934

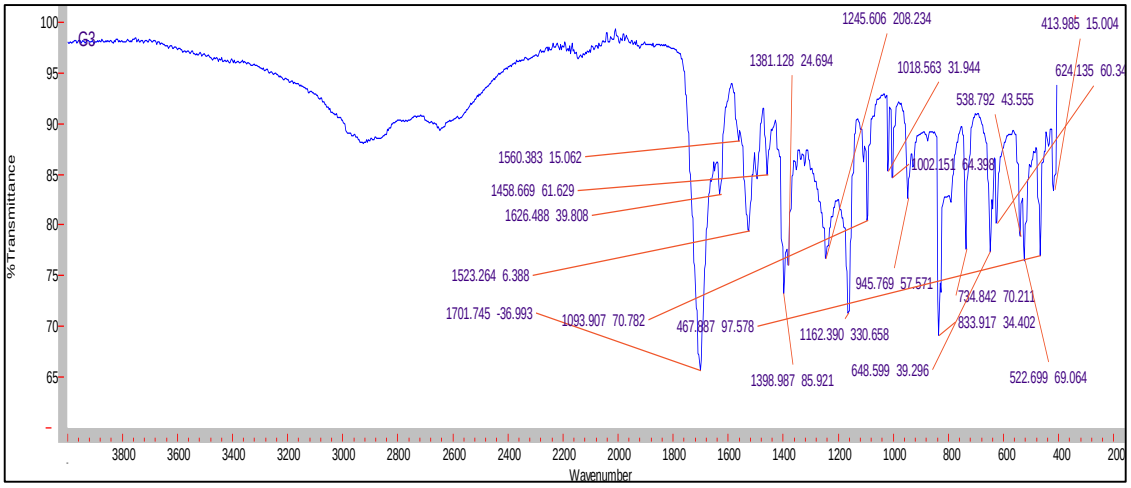

Fig 4: FT-IR Spectra of physical mixture of baclofen and carbopol 934

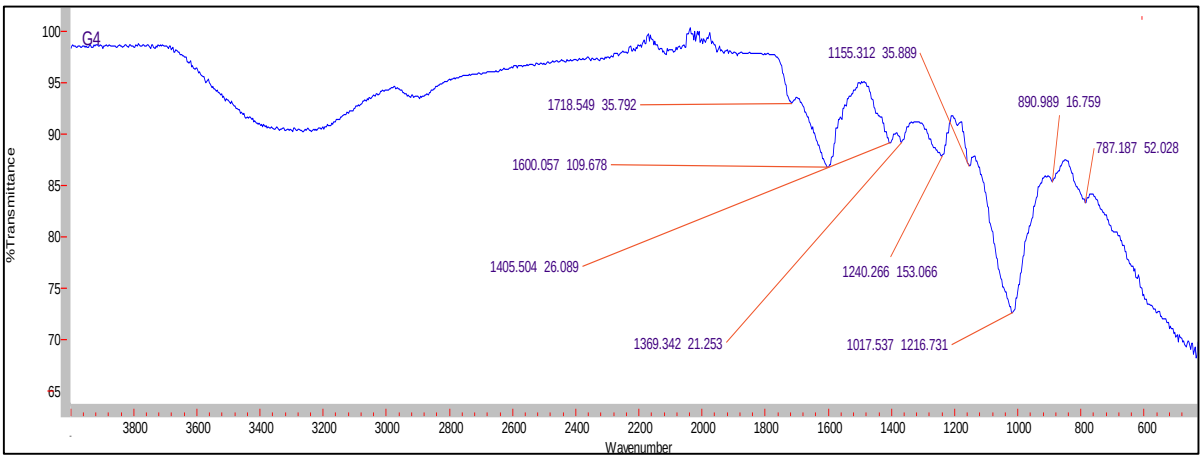

Fig 5: FT-IR Spectra of Xanthum gum

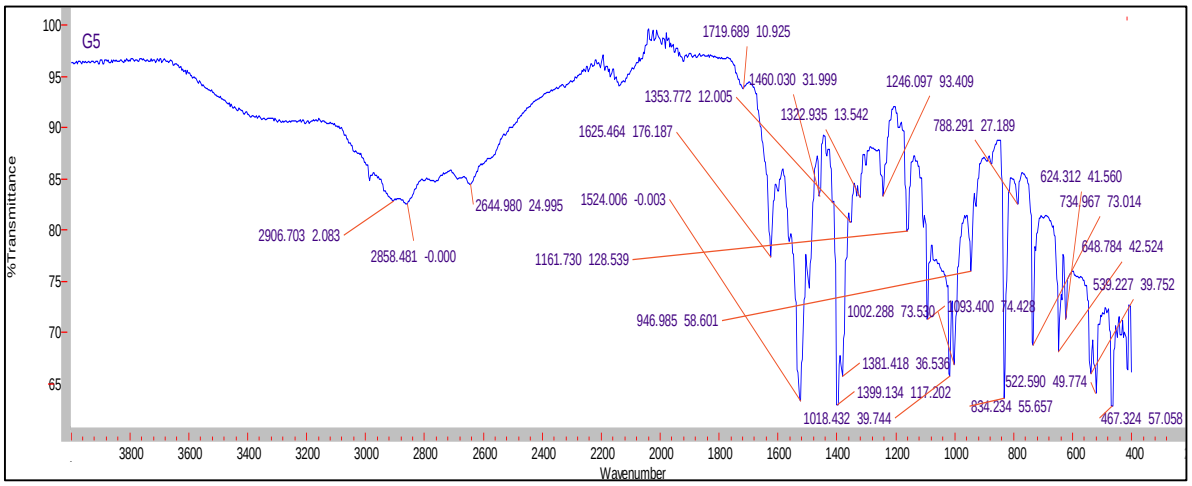

Fig 6: FT-IR Spectra of physical mixture of pure drug and Xanthum gum

Table 5: Physical evaluation of all formulations.

Formulation code	Spreadability	Washability	Occlusiveness	Odour
F1	Easy	Washable	No	No
F2	Easy	Washable	No	No
F3	Easy	Washable	No	No
F4	Easy	Washable	No	No
F5	Easy	Washable	No	No
F6	Easy	Washable	No	No
F7	Easy	Washable	No	No
F8	Poor	Washable	No	No
F9	Easy	Washable	No	No
F10	Easy	Washable	No	No
F11	Easy	Washable	No	No
F12	Easy	Washable	No	No
F13	Easy	Washable	No	No
F14	Poor	Washable	Yes	No
F15	Easy	Washable	No	No
F16	Easy	Washable	No	No
F17	Easy	Washable	No	No
F18	Easy	Washable	yes	No

Table 6: pH, phase separation, drug content of all formulations

Formulation code	pH	Phase separation	Color	Drug content
F1	6.20	No	Transparent	96.6±1.8
F2	6.60	No	CW	97.0 ±1.2
F3	6.34	No	Transparent	94.3 ±0.9
F4	6.44	No	Transparent	95.8 ±1.8
F5	6.81	No	Transparent	98.7 ±1.1
F6	6.26	No	Transparent	92.8 ±1.7
F7	6.34	No	Transparent	97.4 ±1.2
F8	6.38	No	Transparent	98.3 ±1.4
F9	6.61	No	Transparent	96.9 ±1.7
F10	6.42	No	Transparent	98.1 ±0.9
F11	6.47	No	Transparent	99.5±1.4
F12	6.48	No	Transparent	97.2±1.4
F13	6.29	No	Transparent	99.2 ±1.1
F14	6.35	No	Transparent	94.8 ±1.6
F15	6.31	No	Transparent	98.9±1.2
F16	6.69	No	Transparent	98.1 ±1.7
F17	6.80	No	Transparent	99.5±1.5
F18	6.26	No	CW	98.8 ±1.8

Table 7: *In vitro* drug permeation profiles of baclofen controlled release topical gel, (F1-F4)

Time (hrs)	Cumulative amount of drug permeated (µg/cm²/hr)			
	F1	F2	F3	F4
0	0	0	0	0
0.5	86.35±1.43	64.76±1.44	198.14±1.27	188.89±2.1
1	227.44±1.87	105.62±1.49	375.46±1.33	319.95±1.8
2	327.66±1.26	175.01±1.77	463.36±1.45	435.60±1.22
4	408.62±1.89	308.39±1.39	551.25±1.63	605.22±1.59
6	535.83±2.3	431.75±1.27	655.33±1.25	662.27±1.91
8	604.45±1.67	524.88±1.71	659.19±1.19	663.04±1.83
10	634.52±1.31	574.38±1.33	-	-
12	661.50±1.56	660.73±1.92	-	-
18	-	663.81±1.26	-	-

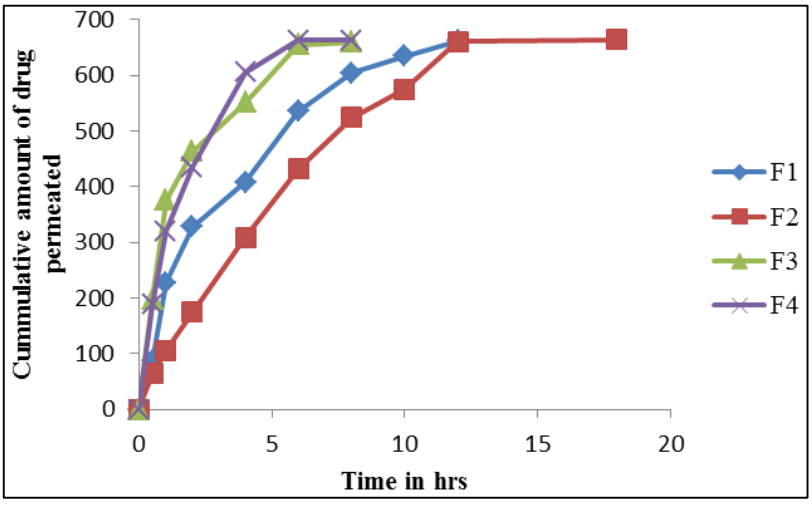

Fig 7: *In vitro* drug permeation profiles of baclofen controlled release topical gel (F1-F4)

Table 8: *In vitro* drug permeation profiles of formulations (F5-F8)

Time (Hrs)	Cumulative amount of drug permeated (µg/cm²/hr)			
	F5	F6	F7	F8
0	0	0	0	0
0.5	111.79±1.9	163.44±1.67	198.91±1.15	215.87±1.07
1	196.60±2.1	227.44±1.51	319.18±1.95	323.04±2.05
2	304.53±2.4	296.82±1.63	535.06±1.29	412.47±2.23
4	373.92±1.85	419.41±2.0	616.01±1.74	515.01±1.87
6	475.69±1.71	501.91±1.44	661.50±1.86	599.05±2.65
8	608.30±2.2	660.73±2.3	-	635.29±2.43
10	658.42±2.7	-	-	661.50±1.71
12	-	-	-	-

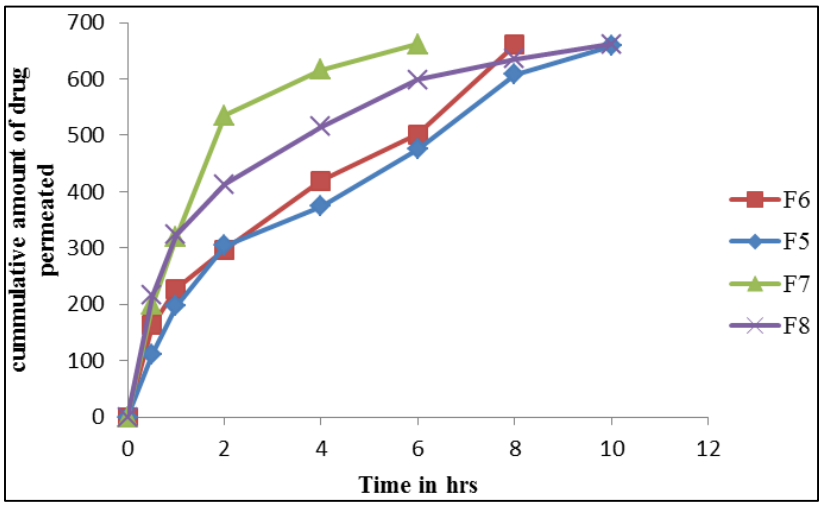

Fig 8: *In vitro* drug permeation profiles of formulations (F5-F8)

Table 9: *In vitro* drug permeation profiles of formulations (F9-F12)

Time (Hrs)	Cumulative amount of drug permeated (µg/cm²/hr)			
	F9	F10	F11	F12
0	0	0	0	0
0.5	71.23±1.58	167.60±1.88	121.51±1.99	137.43±1.52
1	93.85±1.14	290.96±1.39	230.45±1.71	264.81±1.75
2	165.92±1.44	421.02±1.48	305.04±1.83	351.97±1.14
4	229.61±1.67	526.28±2.2	398.06±1.66	461.24±1.78
6	260.62±1.05	602.70±1.73	512.03±1.38	526.28±1.10
8	355.32±1.82	661.70±1.43	602.54±1.22	588.62±1.86
10	501.13±1.54	-	661.20±1.07	642.26±1.25
12	620.13±1.78	-	-	663.04±1.39
18	662.87±1.48	-	-	-
20	-	-	-	-

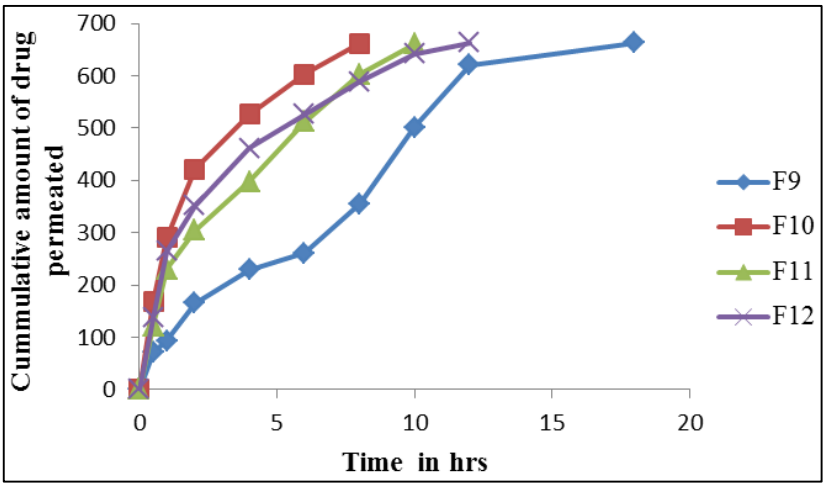

Fig 9: *In vitro* drug permeation profiles of formulations (F9-F12)

Table 10: *In vitro* drug permeation profiles of formulations (F13-F15)

Time (Hrs)	Cumulative amount of drug permeated (µg/cm²/hr)		
	F13	F14	F15
0	0	0	0
0.5	179.33±1.76	289.11±1.38	307.55±1.36
1	272.35±1.29	336.04±1.80	359.51±1.83
2	296.66±1.44	341.07±1.39	481.86±1.55
4	313.42±2.66	406.44±1.74	489.40±1.47
6	377.94±1.03	448.34±1.46	572.37±2.07
8	419.85±1.17	494.43±1.73	594.99±2.50
10	447.50±1.60	551.42±1.89	615.11±2.20
12	470.97±1.58	595.78±2.83	628.60±1.66
18	572.37±1.84	649.32±1.19	661.20±2.54
20	614.27±1.71	662.04±1.29	-
22	643.60±1.59	-	-
24	662.87±2.08	-	-

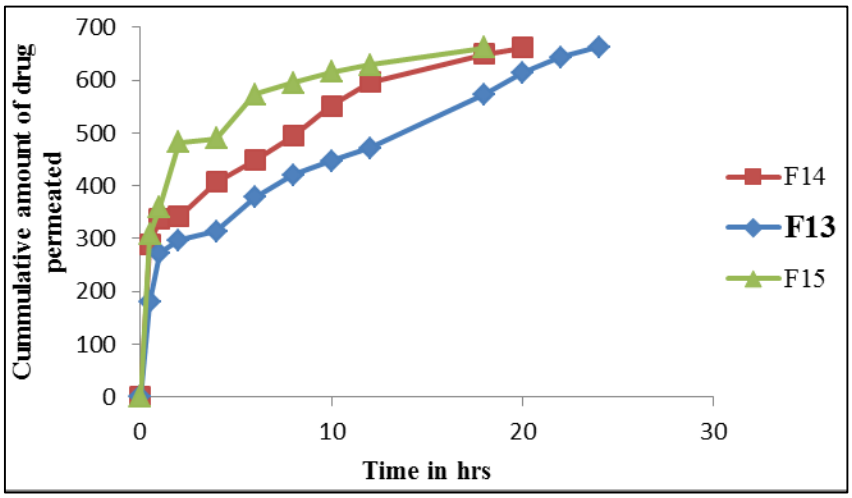

Fig 10: *In vitro* drug permeation profiles of formulations (F13-F15)

Table 11: *In vitro* drug permeation profiles of formulations (F16-F18)

Time (Hrs)	Cumulative amount of drug permeated (µg/cm²/hr)		
	F16	F17	F18
0	**0**	0	0
0.5	132.74±1.74	83.26±1.58	150.84±2.8
1	201.79±2.04	138.00±1.2	186.04±2.4
2	277.55±2.08	195.83±1.69	250.56±1.8
4	335.21±1.33	230.52±1.71	316.77±1.1
6	394.20±1.61	289.89±1.2	366.21±2.6
8	438.45±1.28	333.83±2.2	417.33±2.2
10	482.03±1.79	384.72±2.6	448.34±1.8
12	532.31±2.50	430.20±1.5	492.75±1.4
18	646.95±1.85	598.28±2.7	600.02±2.9
20	661.70±2.64	632.58±1.9	642.70±1.4
22		648.48±2.10	661.20±1.8
24		659.19±2.70	661.0± 1.2

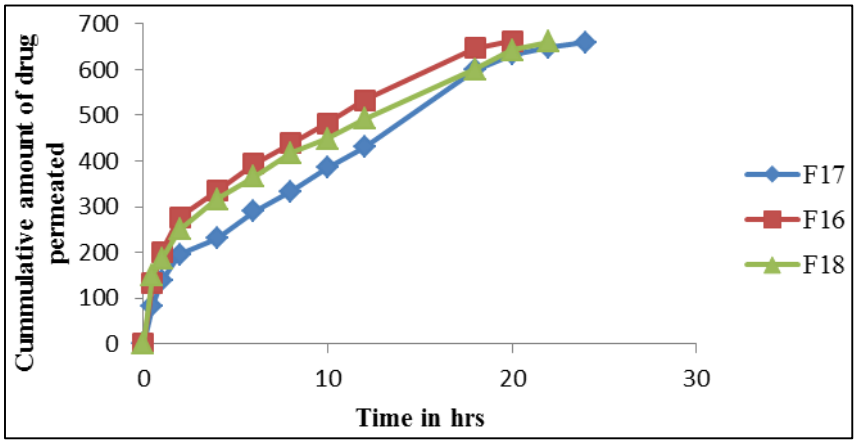

Fig 11: *In vitro* drug permeation profiles of formulations (F16-F18)

Table 12: *In vitro* drug release profiles of formulations (F13, F17 and F18).

Time (hrs)	% Cummulative drug released		
	F13	F17	F18
0	0	0	0
0.5	45.95±1.84	23.98±1.21	25.75±1.28
1	53.78±1.58	38.63±1.37	31.31±1.92
2	55.80±1.24	43.43±1.42	35.10±1.42
4	68.43±1.09	46.46±1.59	37.12±1.58
6	71.46±1.35	61.36±1.38	58.08±1.37
8	71.71±1.99	70.95±1.29	62.37±1.42
10	72.97±1.41	72.22±1.41	70.70±1.79
12	75.75±1.26	79.04±1.56	84.34±1.56
22	88.38±1.34	89.39±1.39	99.74±1.69
24	98.98±1.29	96.46±1.47	-

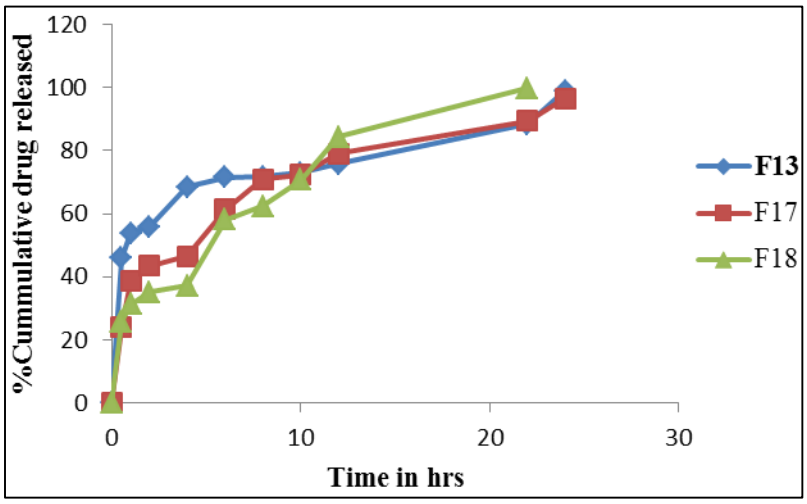

Fig 12: *In vitro* drug release profiles of formulations (F13, F17and F18).

Table 13: Regression analysis and correlation coefficient 'r' values of the *in vitro* release data according to various release kinetic model.

Model fitting	Formulations		
	F13	F17	F18
Zero order	0.561	0.718	0.808
First order	0.776	0.993	0.626
Higuchi matrix	0.773	0.915	0.965
Korsemeyer-Peppas	0.875	0.537	0.420
Hixson crowell	0.831	0.938	0.975

Table 14: *Ex vivo* permeation profiles of formulations F13, F17 and F18

Time (Hrs)	Cumulative amount of drug permeated(µg/cm^2/hr)		
	F13	F17	F18
0	0	0	0
0.5	238.83±0.98	208.66±1.76	138.00±1.74
1	258.11±1.46	304.20±1.37	166.53±1.88
2	288.28±1.21	330.18±1.45	217.41±1.63
4	434.09±1.42	461.75±1.69	255.96±1.25
6	470.13±1.17	506.16±2.19	448.71±1.81
8	489.40±1.85	538.01±2.35	495.74±1.99
10	501.97±1.73	545.55±2.48	521.95±2.05
12	512.87±1.29	563.15±1.62	535.06±1.85
22	601.70±1.55	640.25±2.03	659.96±2.96
24	662.87±1.38	649.47±2.86	659.00±1.9

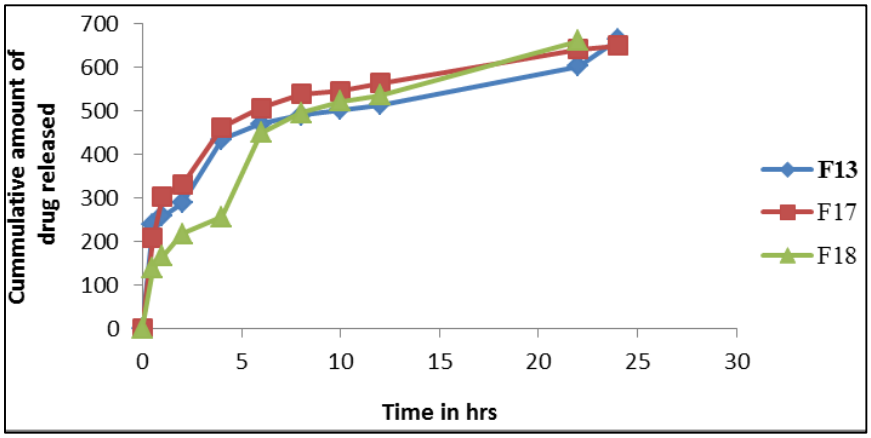

Fig 13: *Ex vivo* permeation profiles of topical gel of baclofen.

Table 15: Stability studies of optimized formulations (F13) at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	pH	Physical appearance	Cumulative amount of drug permeation
0	98	6.29	No change in color	662.24
90	97.1	6.29	Slight yellowish color	661.95

4. Conclusion

Results revealed that prepared gel systems showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F13 formulation was found to be stable as there was no drastic change in the physicochemical properties. Thus conclusion can be made that stable topical hydrogels of baclofen has been developed. F13,F7 formulations showed highest cumulative percentage drug release of 98.98%, 96.46% were obtained during *in vitro* drug release studies after 24 hrs. And F18 formulation showed 99.74% after 22 hr. The release of baclofen appears to be dependent on concentration of polymer. High viscous polymeric network showed showed best release. He high viscosity of the gel system acts as a barrier in between the drug and site of absorption (skin).The predominant release mechanism of drug through the hydrogel was believed to be by diffusion mechanism. During the *in vitro* drug permeation study conducted on F13, F17 and F18 formulation showed cumulative amount of drug permeation of 662.87, 659.19, 661.20 µg/cm$^{2/}$hr respectively. The *ex vivo* skin permeation studies were conducted on F13, F17and F18 formulations, the F13 formulation exhibited high (662.87) cumulative amount of drug permeation through abdominal rat skin when compare with other formulations i.e. F17(649.47), F18(659.96). The F13 formulation showed flux of 4.2743 µg/cm^2/hr with permeability coefficient of Kp 1.4247. Based upon the *in vitro* dissolution data and *in vitro* drug permeation data the F13, F17 and F18 formulations showed similar drug release but upon *ex vivo* permeation studies it was found that F13 formulation showed superior drug release, therefore F13 formulation was concluded as optimized formulation.

5. References

1. Ferry John D. Viscoelastic Properties of Polymers. New York: Wiley, 1980. ISBN 0471048941.
2. GEL. rinceton. edu. Retrieved 2012-01-07. By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid. It is the crosslinks within the fluid that give a gel its structure (hardness) and contribute to stickiness (tack).
3. Richard Jones G, Edward Wilks S, Val Metanomski W, Jaroslav Kahovec, Michael Hess, Robert Stepto *et al*. Compendium of Polymer Terminology and Nomenclature (IUPAC Recommendations 2008)("The Purple Book") (2nd ed.). RSC. 2009, 464. ISBN 978-0-85404-491-7.
4. Vyas SP, Khar RK. Targetted and controlled Drug Delivery Novel carrier system1st ed. CBS Publishers and distributors, New Delhi, 2002, 411-447.
5. Shwe Zin Nyunt Ma. Topicalaspirin gel formulation and assessment of its irritancy in an vivo model.
6. Cleek RL, Bunge AL. A new method for estimating dermal absorption from chemical exposure. General approach, Pharm Res. 1993; 10:497-506.
7. Hadgraft J, Guy R. In; Transdermal Drug Delivery, Marcel Dekker, Inc., New York and Basel, 35, 296.
8. Misra AN, In; Jain NK Eds. Controlled and Novel Drug Delivery, 1st ed. CBS Publishers and Distributors, New Delhi, 2002, 101-107.
9. Ghosh TK, Pfister WR. Transdermal and Topical Drug Delivery Systems, Int. Pharm., Press, 39.
10. Berner B, John VA. Pharmacokinetic characterization of transdermal delivery systems. Clinical pharmacokinetics. 1994; 26(2):121-34. PMID 8162656.
11. Breathnach AS. An Atlas of the Ultrastructure of Human Skin. London: Churchill, 1971.
12. Roberts MS. Targeted drug delivery to the skin and deeper tissues: role of physiology, solute structure and disease. Clin Exp Pharmacol Physiol. 1997; 24(11):874-9.
13. Jasti BR, Abraham W, Ghosh TK. Transdermal and Topical drug delivery systems. In: Ghosh TK, Jasti BR, editors. Theory and Practice of Contemporary Pharmaceutics. 1st ed. Florida: CRC Press, 2005, 423-53.
14. Brahmaiah B, Sasikanth Kothamasu, Sreekanth Nama. Formulation and evaluation of extended release mucoadhesive microspheres of Rosuvastatin, International Journal of Biological & Pharmaceutical Research, e-ISSN NO-0976-3651, Print ISSN NO-2229-7480, 2013; 4(4):271-281.
15. Brahmaiah Bonthagarala, Sreekanth Nama, Leela Madhuri Pola. Enhancement of Dissolution Rate of Ciprofloxacin by Using Various Solid Dispersion Techniques, International Journal of Pharmaceutical Sciences and Research, ISSN: 0975-8232, IJPSR. 2013; 4(11):4376-4383.
16. Brahmaiah B, Prasanna Kumar Desu, Sreekanth Nama, Satish Babu S. Formulation and evaluation of extended release mucoadhesive microspheres of simvastatin, International Journal of Pharmaceutical and biomedical Research, ISSN No. 0976-0350, 2013; 4(1):57-64.
17. Venkatraman S, Davar A, Chester A, Kleiner L, Wise DL. An overview of controlled release systems, Handbook of Pharmaceutical Controlled Release Technology, New York, Marcel Dekker, Inc. 2000, 431-465.
18. Qiu Y, Zhang G, Wise DL. Research and Development Aspects of Oral Controlled-Release Dosage Forms, Handbook of Pharmaceutical Controlled Release Technology, New York, Marcel Dekker, Inc. 2000, 465-503.
19. Berner B, John VA. Pharmacokinetic characterization of transdermal delivery systems. Clinical pharmacokinetics. 1994; 26(2):121-34. PMID 8162656.
20. Jasti BR, Abraham W, Ghosh TK. Transdermal and Topical drug delivery systems. In: Ghosh TK, Jasti BR, editors. Theory and Practice of Contemporary Pharmaceutics. 1st ed. Florida: CRC Press, 2005, 423-53.