IJPSR (2012), Vol. 3, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 July, 2012; received in revised form 24 August, 2012; accepted 28 October, 2012

COMPARATIVE STUDIES ON POVIDONE-IODINE OINTMENT AND GEL

T. Mangilal*[1], K. S. K. Rao Patnaik [2], R. Sivakumar [3], Y. Sudhakar [4] and S. K. Basu [5]

Department of Pharmacy, University College of Technology, Osmania University [1], Hyderabad-500 007, Andhra Pradesh, India
Faculty of Pharmacy, Pharmaceutical sciences, Osmania University [2], Hyderabad - 500 007, Andhra Pradesh, India
Geethanjali College of Pharmacy, Department of Pharmaceutical Chemistry [3], Cheeryal (V), Keesara (M), RR. Dist, Hyderabad- 501 301, Andhra Pradesh, India
Government Polytechnic for Women [4], Kadapa - 516 002, Andhra Pradesh, India
Department of Pharmaceutical Technology, Faculty of Engineering and Technology, Jadavpur University [5], Kolkata – 700 032, West Bengal, India

Keywords:
Antimicrobial activity, Gel, Ointment, Povidone-iodine, Wound healing

Correspondence to Author:

T. Mangilal

Senior Research Fellow, Department of Pharmacy, University college of Technology, Osmania University, Hyderabad-500 007, Andhra Pradesh, India

E. Mail: teelavath@gmail.com

ABSTRACT

Povidone-Iodine Ointment was prepared using polyethylene glycol base by fusion method and the gel was prepared using Poloxamer 407 as a gelling agent by cold process. The different characteristics of povidone-iodine ointment and gel were compared from the results obtained for assay and total, available and complex iodine contents. These values were comparable with marketed formulations. The formulations were tested for wound healing and antimicrobial activity. Wound healing studies show that the time taken for complete wound healing was slightly less for prepared povidone-iodine ointment and gel than the marketed preparations. Antimicrobial activity also found to be almost equal for the different formulations.

INTRODUCTION: The superiority of Iodine Compared to others substances using a considerable number of different preparations at different concentrations in topical antisepsis has been indicated by a mixture of laboratory, animal and human studies. Iodine has been shown to be the only agent that is simultaneously active against gram positive, gram negative, spores, amoebic cyst, fungi, protozoa, yeasts and Methicillin resistant *staphylococcus aureus* [1, 2, 3]. Though iodine possesses the above beneficial property, its adverse side effects, painfulness of open wounds and the possibility of allergic reactions limit it, use as such. Consequently a number of iodine compounds and preparations were developed with the objective of overcoming its disadvantages without significant loss of germicidal activity [4]. Among them iodophors such as Povidone-Iodine have been successfully employed for therapeutic applications.

Povidone-Iodine was introduced to the Pharmaceutical Market as antiseptic agent and is as effective as iodine and its effectiveness has been clinically proven for all types of topical applications in human medicine.

Topical application of Povidone-Iodine useful and effective in the treatment of burns and infected skin ulcers were control of bacterial growth or maintenance of low bacterial count along with protection of developing epithelium is essential [5].

QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Website:
www.ijpsr.com

Povidone-Iodine can be used on mucous membranes without the danger of burns, and it is not only antiseptic but also appears to augment wound healing [6]. It has been shown to be effective, fast acting and a safe wound healing disinfectant [7]. The problems arising due to growing resistance against other antibiotic and antiseptics and existence of cross-resistance among them should turn as to the use of Povidone-Iodine.

Newer formulations providing a great improvement (not zeopardizing proliferation of fibroblast and epithelial cells and neither collagen production) in wound healing. Thus, newer vehicle might actually enhance the wound healing process. Among the newer formulations single-phase Gels have certain advantages like, high degree of clarity, ease of applications and removal [8,9]. They often provide a faster release of drug substance independent of its aqueous solubility compared to creams and ointments.

Keeping the above facts in mind it was thought worthwhile to develop Topical dosage forms, namely ointment and gel of Povidone-Iodine and compare its characteristics with available Marketed Preparations. The aim and objective of the present investigation was to develop and evaluate topical preparations of povidone-iodine, namely ointments and gels and to compare their characteristics with existing marketed preparations.

MATERIALS AND METHODS:

Materials: The materials were obtained from the indicated suppliers and used as received. Povidone-Iodine (Drakt Pharmaceuticals, Vadodara, India.), Polyethylene Glycols 400 and 4000 (S.D Fine-Chem Pvt Ltd, Boisar, India.), Lutrol® F 127 (BASF India Ltd, Hyderabad, India.), Sodium thiosulphate Crystals (Merck Limited India), Soluble starch (Merck Limited India), Sodium bisulphate (Glaxo chemical laboratories, India.), Ferric Ammonium Sulphate (Apex chemicals and Co Ltd, India.), Silver nitrate (Buche Laboratories Ltd, India.), Potassium Iodide and Potassium Iodate (Merck Limited India), Sodium chloride (Sisco Research Laboratory Pvt Ltd, India.), Ammonium thiocyanate (Sisco Research Laboratory Pvt Ltd, India.), Sodium hydroxide (Merck Limited India), Iodine (Sisco Research Laboratory Pvt Ltd, India.), Hydrochloric Acid (Sisco Research Laboratory Pvt Ltd,India.), Nitric Acid (Sisco Research Laboratory Pvt Ltd, India), Sodium Carbonate (International Chemical Industries, India), Sulphuric acid (Sisco Research Laboratory Pvt Ltd, India.), Ethyl Alcohol 75% (Eastern Distilleries chemicals Ltd, India), Agar-Agar and Peptone (Qualigens Fine Chemicals, India), Beef Extract (Merck Limited, India).

Methods: A solution of 0.1 M Sodium thiosulphate [10], 0.1 N Silver nitrate [11], 0.1 N Ammonium thiocyanate [12] was prepared and standardized

Analysis of Povidone-Iodine Raw Material:

Assay: Weigh accurately about 3 g of Povidone-Iodine, transfer to a beaker and add 200 ml of water cover the beaker and stir with a mechanical stirrer at room temperature for not more than 1 hour to dissolve as a completely as possible. Titrate immediately thereafter with 0.1 M Sodium thiosulphate using 3 ml of starch solution, added towards the end of the titration as indicator [11]. Each ml of 0.1 M sodium thiosulphate is equivalent to 0.01269 g of Iodine

Determination of Total Iodine: Dissolve about 500 mg of Povidone-Iodine, accurately weighed, in 100 ml of water in a 25 ml conical flask. Add Sodium bisulphate until the colour of Iodine has disappeared. Add 25 ml of 0.1 N Silver nitrates Vs 10 ml of nitric acid, and mix. Titrate the excess Silver nitrate with 0.1 N Ammonium thiocyanate VS, using ferric ammonium sulfate TS as the Indicator. Perform a blank titration [11]. Each ml of 0.1 N Silver nitrate is equivalent to 0.01269 g of Iodine.

Determination of available Iodine: Place about 5 g of Povidone –Iodine, accurately weighed in a 400 ml beaker, and add 200 ml of water, cover the beaker, and stir by mechanical means at room temperature for not more than 1 hour to dissolve as completely as possible. Titrate immediately with 0.1 N Sodium thiosulphate VS, adding 3 ml of starch TS as the end point is approached. Perform a blank determination, and make any necessary correction [12]. Each ml of 0.1 N Sodium thiosulphate is equivalent to 0.01269 g of Iodine.

Determination of Complex Iodine:

Percentage of Complex Iodine = % of Total Iodine - % of Available Iodine

Preparation of Povidone-Iodine Ointment by Fusion Method [13]:

Formula for 100 g

Ingredients	Quantity
Povidone- Iodine 30/06 (BASF)	10 g
Lutrol E 400 (1)	60 g (44.64 ml)
Sodium hydroxide Solution 1 M	4.60 g
Water	0.40 g
Macrogol 4000 II	25 g

Preparation of Povidone -Iodine Gel by Cold Process [10]:

Formula for 100 g

Ingredients	Quantity
PVP-Iodine 30/06	10.0 g
Sodium chloride	1.0 g
Lutrol® F 127	20.0 g
Sodium hydroxide 1 M	7.9 g
Water	70.0 g

Analysis of Formulation:

Assay: Transfer and accurately weighed 5 g of ointment, equivalent to about 50 mg of iodine, to a 100 ml beaker, add water to make a total volume of not less than 30 ml, and stir until the ointment is dissolved. Titrate immediately with 0.02 N sodium thiosulphate, determining the end point potentiometrically, using a platinum calomel electrode system. Perform a blank determination, and make any necessary correction [11]. Each ml of 0.02 N sodium thiosulphate is equivalent to 0.02538 g of Iodine.

Determination of Total Iodine: Dissolve 5 g of Povidone-Iodine Ointment in 100 ml of water in a 250 ml conical flask Add sodium bisulfate TS until the color of Iodine has disappeared. Add 25 ml of 0.1 N silver nitrates VS 10 ml of nitric acid, and mix. Titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS, using ferric ammonium sulfate TS as the indicator. Perform a blank determination. Each ml of 0.1 N silver nitrate is equivalent to 0.01269 g of Iodine.

Determination of Available Iodine: Place about 50 g of Povidone-Iodine Ointment in a 400 ml beaker, and add 200 ml of water, cover the beaker, and stir by mechanical means at room temperature for not more than 1 hour to dissolve as completely as possible. Titrate immediately with 0.1 N sodium thiosulphate VS, adding 3 ml of starch TS as the end is approached. Each ml of 0.1 N sodium thiosulphate is equivalent to 0.01269 g of Iodine [12].

Determination of Complex Iodine:

Percentage of Complex Iodine = % of Total Iodine - % of Available Iodine

The same method was followed to analyse povidone-iodine gel, marketed ointment, marketed gel and stability samples to determine assay, total iodine, available iodine and complex iodine.

Stability study of Povidone-Iodine Ointment and Gel: Ten batches of Povidone-Iodine ointment were prepared as per BASF Formula. Three batches were taken for stability study. These batches were kept in hot air oven at 52°C for 14 days and analyzed. Stability testing was done by using freeze thaw cycling method, the temperature was altered every 24 hours between 25°C and 5°C for five cycles and samples were observed for physical stability and synergies (spontaneous contraction of gel exuding some of the fluid medium) then analysed [14].

Study for Compatibility of Povidone-Iodine Ointment and Gel with container: Formulations (ointment and gel) were filled in collapsible aluminum tube. Tubes were filled from the open back end of the tube, opposite from the cap end and stored in room temperature for a period of 60 days at interval of 15, 30, 45 and 60 days. The formulations were studied for change of color, consistency, drug content and therapeutic efficacy. The same observation was done after stability study of the formulations. During observation it was found that there was no significant changes of the formulations as well as containers.

Study of Drug Release from Povidone-Iodine Ointment and Gel: The rate of release of iodine from Povidone-Iodine is ascertained by incorporating a soluble starch in the agar and measuring the coloured zone around the spot where Povidone-Iodine ointment and gel was placed.

Study for Antimicrobial Activity of Povidone-Iodine Ointment and Gel: To assess the antimicrobial activity of a medicaments small amount of the Povidone-

Iodine ointment/gel was placed on the surface nutrient agar contained in a petri dish or alternately in a small cup cut in the agar surface.

Study for Drug Penetration Test: Weighed 2 g of ointments or gels are rubbed over 2 cm^2 areas of the human skin and skin of rabbit ear for a 3 hrs of time. Thereafter the unabsorbed ointment or gel is collected from the skin and weighed. The difference between the two weights roughly represents the amount absorbed. Also after application it was observed for the occurrence of patches, lesions etc., at intervals of 24, 48, 72 and 96 hrs for drug irritant effect.

Wound Healing Study: The experiments were conducted on healthy rabbit of same sex of about 2 kg healthy rabbit (weight about 2-2.5 kg) were used. The para vertebral region just beneath the neck (upper thoracic, dorsally) of each rabbit was considered.

Rabbit were weighed and marked following standard protocol. On the day of testing, hair at the test site of animal was shaved and made ready for testing. The sites were kept exposed and cleaned with 75% ethanol. Individual animals were anesthetized using ketamine hydrochloride Injection I.P. at a rate of 100 mg/kg of body weight by intra peritoneal route and were made ready for aseptic surgery. The surgical procedure was performed in an aseptic room. Skin incision of appropriate size was made, with the help of a surgical blade, on shaved test sites and the animal's skin layers were removed. The excised part was rinsed with normal saline solution. The ointment and gels was applied over the excised part of animals and observed for wound healing. After application of ointment and gels observation was done for wound healing.

RESULTS AND DISCUSSION:

Formulation and Analysis: Povidone-Iodine Ointment was prepared by fusion method. 1 M Sodium hydroxide solution was used in the formula as pH modifier. The prepared ointment had a pH of 4-6, miscible and washable with water. The ointment so prepared was subjected to different studies. Also polyethylene glycol was chosen as the suitable ointment base for - uniform distribution of PVP-Iodine in the ointment base, nature of its water solubility, readily miscible with tissue exudates, either penetrate or dissolve and release the medication effectively and not support microbial growth. This may be useful in the treatment of certain conditions using povidone-iodine preparation like infected skin ulcers, where the maintenance of low bacterial count is of important.

Povidone-Iodine gel was prepared by cold process. 1 M Sodium hydroxide solution was used as pH modifier and the pH of the formulation was maintained between 4-6. Sodium chloride was used in the formulation stimulate the healing of wounds. The reason for choice of Poloxamer 407, a synthetic block copolymers of ethylene oxide and propylene oxide (Lutrol F 127) as the gelling agent in the formulation are: primarily as a thickening agent and gel former, its non ionic in nature, thermo reversible, exhibit maximum viscosity in the 30-60°C range, it possesses a unique property of remaining dissolved in water at temperature below ambient temperature and the soluble gel occurring near room temperature. This property is of great advantage for the formulation of topical preparations.

In **Table 1**, the different characteristics of povidone-iodine ointment and gel were compared from the results obtained for assay and total, available and complex iodine contents. There was no major difference between povidone-iodine ointment and gel with respect to the above mentioned characteristics.

Analysis of the povidone-iodine ointment and gel for content of total, available and complex iodine after subjection to stability studies indicate that there was a very slight reduction the total, available and complex iodine. In **Table 2**, these values were compared with marketed formulations. The results indicate that the prepared povidone-iodine ointments and gels formulations may be equally effective as the marketed formulations on the basis of the available iodine.

Compatibility Study: The formulations were studied for compatibility with storage containers. Both ointment and gel before and after the stability studies did not shown any visible interaction between the formulations and container during a period of 60 days.

Drug Release and Antimicrobial Activity: For the drug release study a total blue colour zone of diameter 12 mm (Including a diameter of 8 mm of the cup in the agar plate) was observed for the different formulations studied. This indicates the diffusion release of

povidone-iodine from the different formulations. The different formulations showed comparable drug release. The zone of Inhibition for the different formulations was also found to be almost equal for its antimicrobial activity.

Drug Penetration Test: The formulations were studied for the penetration (absorption) through animal and human skin. The result reveals that the penetrations of the formulations through animal (rabbit) and human skin is almost same in different formulations studied. In Table 2, comparing the penetration property of different formulations including marketed formulations it was found that all the formulations shows similar pattern of absorption. In all preparations the percentage of absorption was found to be above 95% indicating high level of penetration through animal (rabbit) and human skin. This property is suitable for their use in treatment of burns and skin ulcers where the microbial infection is deep seated.

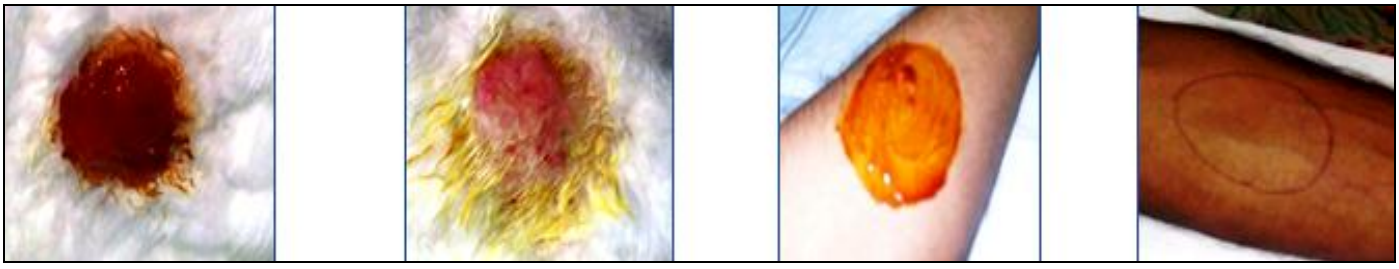
TABLE 1: COMPARISON OF ASSAY, TOTAL IODINE, AVAILABLE AND COMPLEX IODINE IN POVIDONE-IODINE OINTMENT AND GEL

S. No.	Name of the Formulations	Assay	% of total iodine	% of available iodine	% of complex iodine
			Before stability study		
1	Povidone-Iodine ointment	0.48018	0.59982	0.46919	0.13066
2	Povidone-Iodine Gel	0.47206	0.58598	0.46792	0.11806
			After stability study		
1	Povidone-Iodine ointment	0.47207	0.58598	0.46792	0.11806
2	Povidone-Iodine Gel	0.46191	0.57676	0.46538	0.11138

TABLE 2: PERCENTAGE ABSORPTION OF DIFFERENT OINTMENTS AND GELS INCLUDING MARKETED PREPARATION IN RABBIT AND HUMAN SKIN

S. No.	Name of the Formulations	% of absorption on animal skin	% of absorption on human skin
1	Marketed Ointment	97.5	97.7
2	Marketed Gel	97.4	97
		Before Stability	
3	Povidone-Iodine Ointment	98	97.5
4	Povidone-Iodine Gel	97.5	97.25
		After Stability	
5	Povidone-Iodine Ointment	98	96.5
6	Povidone-Iodine Gel	97.7	97.75

Drug Irritant Effect: Figures 1a-d shows the prepared formulations were studied for irritation on animal skin as well as human skin. There was no evidence of patch or lesions on the ointment and gel applied skin. This result indicates that there is no irritation effect of the formulations on the applied skin. This is valuable since povidone-iodine is used in conditions where significant injury or destruction of normal human skin has occurred.



1A **1B** **1C** **1D**

FIG. 1A: APPLICATION OF OINTMENT/GEL ON RABBIT SKIN; FIG. 1B: AFTER APPLICATION OF OINTMENT/GEL ON RABBIT SKIN; FIG. 1C: APPLICATION OF OINTMENT/GEL ON HUMAN; FIG. 1D: AFTER APPLICATION OF OINTMENT/GEL ON HUMAN SKIN

Wound Healing Effect: Diameter of the created wounds were approximately 3 cm. **Figure 2a-h** shows various stages of wound healing effect of povidone-iodine ointment and gel. Marketed product also tested parallel for comparative purpose. Total wound healing time in all the formulations was observed 13±1 days.

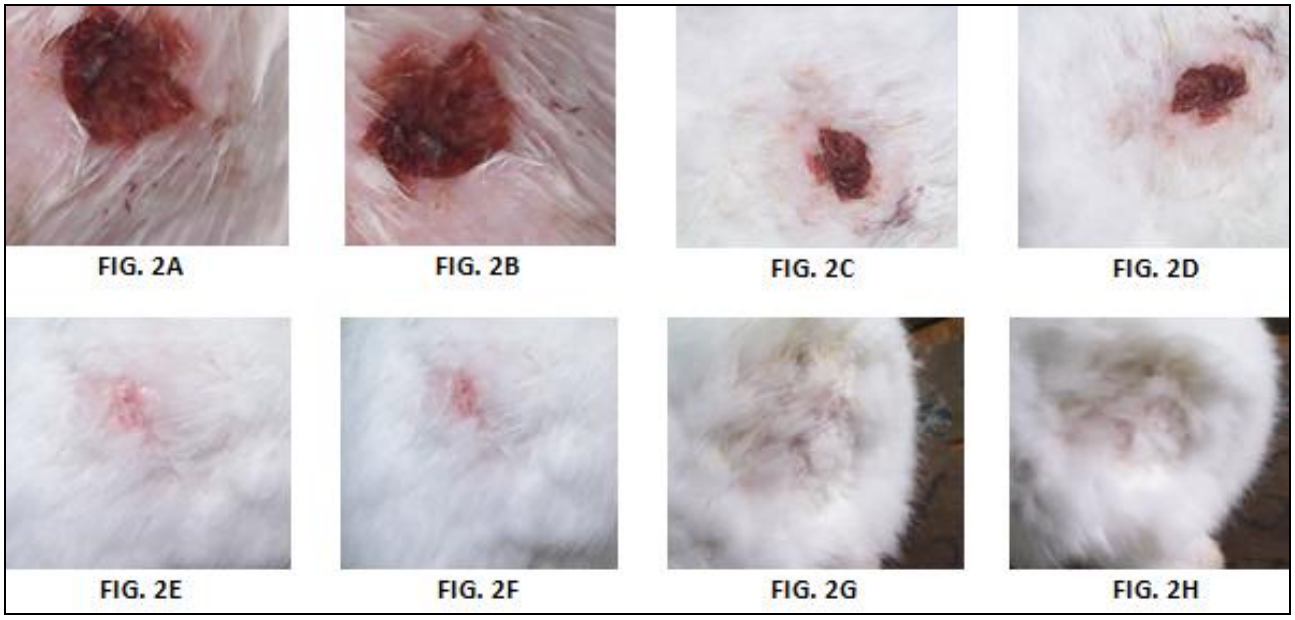


FIG. 2A: INFLAMMATORY PHASE AFTER APPLYING OINTMENT, FIG. 2B: INFLAMMATORY PHASE AFTER APPLYING GEL, FIG. 2C: MIGRATORY PHASE AFTER APPLYING OINTMENT, FIG. 2D: MIGRATORY PHASE AFTER APPLYING GEL, FIG. 2E: PROLIFERATIVE PHASE AFTER APPLYING OINTMENT, FIG. 2F: PROLIFERATIVE PHASE AFTER APPLYING GEL, FIG. 2G: REMODELING PHASE AFTER APPLYING OINTMENT, FIG. 2H: REMODELING PHASE AFTER APPLYING GEL

The wound healing process occurs at four phases. Figures 2a,b shows the first inflammatory phase occurred within 0-3 days, figure 2c,d shows the second destructive/migratory phase occurred within 3-5 days, figure 2e, f shows the third proliferative phase occurred within 6-10 days and figure 2g, h shows the fourth remodeling phase occurs within 10-14 days. In case of marketed preparations, it was observed that the fourth remodeling phase occurred within 14 days, whereas in case of tested formulations showed slightly lesser time for wound healing.

CONCLUSION: Analysis of the povidone-iodine indicated the suitability of the material for use in formulations. Thus povidone-iodine was incorporated in ointment prepared by fusion method and gel prepared by cold process. The prepared ointment and gel had a pH 6 which is essential for the effectiveness of povidone-iodine. The prepared formulations were analysed for different characteristics. The analysis shows that both ointment and gel have almost same assay values. Similarly the percentage of total iodine, available iodine and complex iodine for both the preparations were found to be almost equal (Table 1). Thus it can be said that the prepared povidone-iodine ointment and gel are chemically equivalent in their respective preparations.

The prepared povidone-iodine ointment and gel were subjected to stress studies, analysis and observations for assay, total iodine, available iodine and complex iodine show a very slight decrease in the above values. In addition, no physical instability was observed for the prepared povidone-iodine ointment and gel. So, it can be concluded that the prepared formulations of ointment and gel possess adequate stability. It also showed no visible interaction with the containers in which it was stored indicating no incompatibility problems.

Drug release and antimicrobial studies indicate comparable drug release and antimicrobial activity of the prepared povidone-iodine ointment and gel with that of the marketed preparations (Betadine ointment and Povicidal gel). More than 95% of absorption was observed for the prepared and marketed preparations indicating a high level of penetration through animal and human skin (**Table 2).** This is a desirable property for preparations used in the treatment of burns and skin ulcers where deep-seated microbial infection is present. No irritation effect was observed for different formulations studied on animal and human skin from the irritancy study. Wound healing studies show that the time taken for complete wound healing was slightly less for prepared povidone-iodine ointment and gel than the marketed preparations (Fig. 2a-h).

In conclusion, it can be said the prepared povidone-iodine ointment and gel have comparable characteristics on the different aspects studied and with that of the marketed preparations. Gels have certain advantage like, high degree of clarity, ease of applications and removal. They often provide a faster release of drug substance independent of its aqueous solubility compared to creams and ointments.

REFERENCES:

1. Hammarlund E, Lewis MW, Hanifin JM, Simpson EL, Carlson NE and Slifka MK: Traditional smallpox vaccination with reduced risk of inadvertent contact spread by administration of povidone iodine ointment. Vaccine 2008; 26(3): 430-439.
2. Selvaggi G, Monstrey S, Van Landuyt K, Hamdi M and Blondeel P: The role of iodine in antisepsis and wound management: a reappraisal. Acta Chirurgica Belgica 2003; 103: 241-247.
3. Das Neves J and Bahia MF: Gels as vaginal drug delivery systems: Indian Journal of Pharmaceutical Sciences 2006; 318: 1-18.
4. Aiba M, Ninomiya J, FuruyaK, Arai H, Ishikawa H, Asaumi S, Takagi A, Ohwada S and Morishita Y: Induction of a critical elevation of povidone-iodine absorption in the treatment of a burn patient: report of a case. Surgery Today 1999; 29(2): 157-159.
5. Al-Kaisy Salih AA and Sahib A: Role of the antioxidant effect of vitamin E with vitamin C and topical povidone-iodine ointment in the treatment of burns. Annals of Burns and Fire Disasters 2005; 18(1): 19-30.
6. Monif GR, Thompson JL, Stephens HD and Baer H: Quantitative and qualitative effects of povidone-iodine liquid and gel on the aerobic and anaerobic flora of the female genital tract. *American Journal* of Obstetrics and Gynecology 1980; 137(4): 432-438.
7. Densinger SW, Hans-Uwe Schenck W and Wolfgang Schwarz L: Preparation of polyvinyl pyrolidone iodine. US Patent, 1980, Application Number, 30,900.
8. Kattan E, Asbill AF, Kim CS and Michniak BB: Effect of formulation variables on the percutaneous permeation of ketoprofen from gel formulations. Drug Delivery 2000; 7: 3-8.
9. Zhang L, Parsons DL, Navarre C and Kompella UB: Development and in-vitro evaluation of sustained release poloxamer 407 (P407) gel formulations of ceftiofur. Journal of Controlled Release 2002; 85: 73-81.
10. Beckett AH and Stenlake JB: A text book of practical pharmaceutical chemistry 2002
11. Indian Pharmacopiea. 1996, Vol. II: 190.
12. British Pharmacopoeia. 2003, Vol. II, A 10, 1068.
13. Collett M and Aulton E A: Text Book of Pharmaceutical Practice 2nd Edition 2002.
14. Panda D, Si S, Swain S, Kanungo SK and Gupta R: Preparation and evaluation of gels from gum of Moringa oleifera. Indian Journal of Pharmaceutical Sciences 2006; 68(6): 777-780.

How to cite this article:
Singh S, Mann R and Sharma SK: Phytochemical Analysis and Pharmacognostical Standardization of stem of *Cayratia trifolia* (Linn.) Domin. *Int J Pharm Sci Res*. 3(11); 4507-4513.