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Formulation, Development & Evaluation of Matrix Type Transdermal Patch of Xanthine Oxidase Inhibitor (Allopurinol)

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ABSTRACT

AIM- The aim of the present investigation is to deveope formulation, development and evaluation of Matrix Type Transdermal Patch of Xanthine Oxidase Inhibitor. **MATERIAL & METHODS-** Melting point of drug was determined using digital melting point apparatus by capillary fusion method. The infrared spectroscopy of the pure drug sample was carried out to identity the drug. A pellet of drug was prepared by compressing of the drug with IR grade potassium bromide by applying of 5.5 metric ton of pressures in KBr press. The dissolution and diffusion fluid for drug release and permeation studies respectively were selected based on solubility data of allopurinol in various fluids. The matrix type transdermal patches of allopurinol were prepared by solvent evaporation technique by using different ratio of ethylcellulose (EC) and polyvinylpyrrolidone K-30 (PVP) polymers. The prepared transdermal patch were evaluated by the physical appearance, thickness, weight variation, drug content, moisture content, moisture uptake, tensile strength, flatness etc. **RESULTS-** The melting point of drug sample was found to be 354±1^{0}C which compared with previously reported value (350-355^{0}C) indicated that the drug sample was pure. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{-1} using FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan). The solubility study revealed that the drug sample was freely soluble in methanol, soluble in chloroform and 20% methanol in phosphate buffer solution (PBS) 7.4, sparingly soluble in 10% methanol in PBS pH 7.4, slightly soluble in 5% methanol in PBS pH 7.4 and very slightly soluble in PBS pH 7.4. The weight of transdermal patched varied from 164.37 to 172.01 mg which indicated that the prepared different batches of transdermal films were similar in weight. The thickness of different batches were found in range from 0.246 to 0.276 mm. The percentage of moisture contents and moisture uptake were found in the range from 1.64 ± 0.31 to 6.38 ± 1.04 and 2.43 ± 0.55 to 9.41 ± 0.75 respectively. **CONCLUSION-** The objective of the present study was to

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develop transdermal matrix patch of allopurinol and assess its feasibility for transdermal application.

KEYWORDS-

Formulation & Development, Matrix Type, Transdermal Patch, Xanthine Oxidase Inhibitor, Allopurinol

INTRODUCTION

Transdermal drug delivery systems that can deliver medicines via the skin portal to the systemic circulation at a predetermined rate and maintain clinically effective concentrations for prolonged period of time. This route of drug administration represents an attractive alternative to oral delivery of drugs and avoids the hazards and discomfort associated with parenteral therapy. The treatment can also be terminated rapidly by simply removing the patch when need arises. Transdermal delivery may also eliminate side effects of that drugs cause when presented in conventional forms (Karande and Mitragotri, 2009; Elsayed *et al.*, 2007).

The first three day transdermal patch of scopolamine to treat motion sickness was approved in the United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the public in general. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, nitroglycerin and clonidine for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, testosterone for hypogonadism and oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement (Paudel *et al.*, 2010).

Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery with around 40% of the drug candidates being under clinical evaluation related to transdermal or dermal systems (Alexander *et al.*, 2012).

The objectives of the proposed study are as to develop low dose maintenance therapy of Allopurinol to reduce the risk of potential side effects, improve the patient compliance in gout patients.

MATERIAL & METHODS

Preformulation studies

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Preformulation studies are needed to ensure the development of a stable, therapeutically effective and safe dosage form. It is a stage of development during which the physical pharmacist characterizes the physicochemical properties of drug substance and its interaction with various formulation components.

Physical appearance

The drug sample was purchased from Yarrow Chem Products, Mumbai, India. The supplied powder of drug sample was a crystalline, white to off white in colour powder of odourless and bitter in taste.

Determination of Melting Point

Melting point of drug was determined using digital melting point apparatus by capillary fusion method. A capillary was taken and its one end sealed with the help of burner. The temperature at which drug starts to melt was noted.

Fourier Transform Infrared (FT-IR) Spectroscopy

The infrared spectroscopy of the pure drug sample was carried out to identity the drug. A pellet of drug was prepared by compressing of the drug with IR grade potassium bromide by applying of 5.5 metric ton of pressures in KBr press. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{-1} using FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan) (B.P,2009).

Determination of Solubility

The dissolution and diffusion fluid for drug release and permeation studies respectively were selected based on solubility data of allopurinol in various fluids. The volume of solvent required to dissolve the drug was recorded (Prasanthi and Lakshmi, 2012).

Formulation of Transdermal Patches by Optimized Formula

The matrix type transdermal patches of allopurinol were prepared by solvent evaporation technique by using different ratio of ethylcellulose (EC) and polyvinylpyrrolidone K-30 (PVP) polymers. The polymers EC and PVP were weighed and mixed in different ratios by keeping the total polymers weight at 1.6 g added in a chloroform solvent using magnetic stirrer. The dibutyl phthalate 30% w/w of polymer was incorporated as plasticizer. Drug 20 % w/w of polymer weight was added slowly to the polymers solution and mixed thoroughly by

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continuous stirring for 30 minutes to obtain a homogenous solution. The five formulations were prepared by using same drug and different polymers ratio without permeation enhancer in order to determine the optimum combination of drug and polymers. On the basis of preliminary studies, the optimized polymers ratio 3:2 (EC:PVP) were mixed with the different permeation enhancers like DMSO, Tween-80, eucalyptus oil and olive oil. The permeation enhancers were added in three different concentrations *i.e.* 2%, 5% and 10% w/w of total polymers weight for each. The resulting drug-polymers solution was poured in petridish of 64 cm^2. The aluminum foil was uniformly spread on petridish on which drug-polymers solution was poured. The rate of evaporation was controlled by inverting a funnel over the petridish and the solvent was allowed to evaporate for 24 h at room temperature. After 24 h, the films were collected and a wax paper was applied on other side of the films as a release liner to complete the formulation (Arora and Mukherjee, 2002; Verma and Chandak, 2009).

PHYSICOCHEMICAL EVALUATION OF PATCHES

Physical Appearance

All formulated transdermal patches were visually inspected for colour, clarity, entrapment of any air bubble, flexibility and smoothness, which on a large part determines patient acceptability of the patch and also therapeutic efficacy (John *et al.*,2013).

Thickness

Thickness of transdermal patch was measured by using digital thickness gauge (Muttato Japan). Thickness of rectangular patch (2x2 cm) was determined with a four different points and average thickness was taken. Same was performed for other patches also (Patel e*t al.*, 2009).

Weight Variation

Weight variation study of transdermal patches was performed by individually weighing 10 randomly selected patches of sizes 4.52 cm^2 on digital weighing balance and average weight was calculated. The individual weight of patches should not deviate significantly from the average weight (El-Gendy *et al.*, 2009).

Drug Content

To determine the drug content of transdermal patch, known amounts of patch was cut from

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casted film and dissolve in chloroform in 100 ml volumetric flask and placed in shaking incubator for 4 h. The solution was filtered through membrane filter (0.45 µm) and 1 ml solution was taken and diluted with chloroform to 10 ml. The absorbance of solution was measured by using UV/visible spectrophotometer (Model-1700, Shimadzu, Japan). The chloroform was used as a blank. The average reading of three patches was taken as the content of drug in one patch (Limpongsa and Umprayn, 2008).

Moisture Content

To determine moisture contents of transdermal patches, they were weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The transdermal patches were weighed repeatedly until they showed a constant weight (Bagyalakshmi et al., 2006; Devi *et al*, 2003).

Moisture Uptake

Transdermal patches were kept in desiccators at room temperature for 24 h with silica gel and weighed (w_s) and transfer to other desiccators to expose of 75% RH using a saturated solution of sodium chloride at 25^0C and patches were reweighed again and again, until a constant weight (w_m) was obtained.

Flatness

Longitudinal strips from the 5 randomly selected transdermal films of each formulation were cut out. One from the center and one from the other side of patch. The length of each strip was measured and the variation in length because of the non-uniformity of flatness was measured. 0 % constriction was considered to be 100 % flatness (Chandak & Verma, 2008).

Tensile Strength

The formulated patches were evaluated for its tensile strength to measure their mechanical properties. The tensile strength of the patches was determined by using a self designed assembly. Assembly consists of a pan hanged by using a strong thread and the other end of the thread was attached with the centre of the patch. The whole assembly was held like a beam balance and weights were kept on the pan (Bhatia *et al.*, 2012).

Statistical Analysis

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The formulation parameters were statistical evaluated by Graph pad prism 5 using one-way analysis of variance (ANOVA), followed by Dennett test multiple comparison tests and unpaired t-test. The obtained results were expressed as the mean ± standard deviation.

RESULTS AND DISCUSSION

Identification

The supplied powder of allopurinol was a crystalline, white or almost white in color powder of odorless and bitter in taste. The melting point of drug sample was found to be 354±1^{0}C which compared with previously reported value (350-355^{0}C) indicated that the drug sample was pure.

Table No.1: Physical characteristics of Allopurinol

S. No.	Parameters	Observation	Reference
1.	Physical appearance	Nature: Crystalline solid Colour: White to off white Odour: Odourless Taste: Bitter	Nature: Crystalline solid Colour: White to off white Odour: Odourless Taste: Bitter
2.	Melting point	354±1^{0}C	350-355^{0}C
3.	UV Absorption Maxima (λ_{max})	260 nm	260 nm

The infrared spectroscopy of the pure drug sample was carried out to identity the drug sample. Potassium bromide was used for preparing the sample for I.R. spectroscopic study. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{-1} using FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan). Peaks corresponding to various functional groups are reported in Table 2.

Table No.2: Peaks in I.R. spectrum indicating various functional groups

S. No.	Functional groups	Peak observed (cm-^{1})
1.	Secondary amine stretching	3169
2.	Aromatic CH stretching	3096, 3080, 3046, 3038 and 3019

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3.	Asymmetric CH_2 and CH_3 stretching	2990, 2959, 2922 and 2918
4.	Symmetric CH_2 and CH_3 stretching	2889 and 2854
5.	C-F stretching	1328
6.	C-O stretching Aryl/alkyl ether stretching	1243
7.	C-N stretching	1174 and 1163

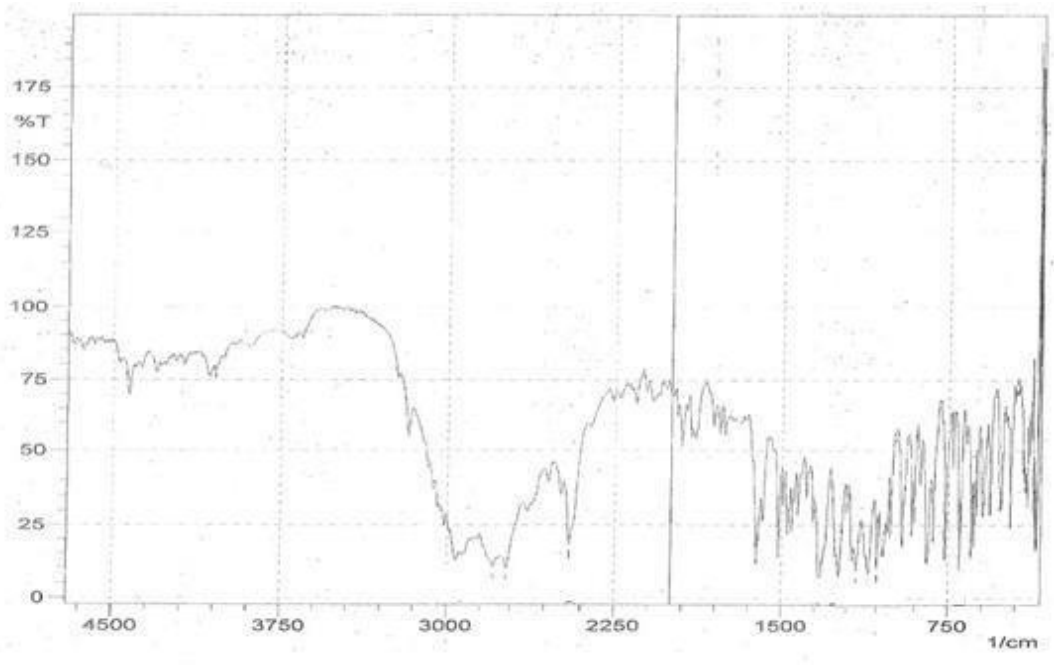

Figure No.1: I.R. spectrum of Allopurinol

Determination of Solubility

Solubility study of drug sample was determined for selection of dissolution and diffusion medium in different solvents at room temperature. The solubility study revealed that the drug sample was freely soluble in methanol, soluble in chloroform and 20% methanol in phosphate buffer solution (PBS) 7.4, sparingly soluble in 10% methanol in PBS pH 7.4, slightly soluble in 5% methanol in PBS pH 7.4 and very slightly soluble in PBS pH 7.4.

Formulation of Transdermal Patches

The transdermal patches were prepared by using ethylcellulose (EC) and polyvinylpyrrolidone K-30 (PVP) polymers in different composition. The EC and PVP are most commonly used polymers in transdermal drug delivery system because of their compatibility with drugs and sustained release properties (Khan *et al.,* 2012). In preliminary studies, various formulations were prepared with or without plasticizer. The transdermal patches prepared without plasticizer were found to be brittle and hence di-n- butyl phthalate was used as plasticizer to reduce the brittleness of the transdermal patches. The

studies indicated that addition of di-n-butyl phthalate at 30% w/w of total dry polymers weight produces smooth, uniform and flexible films. Hence, further formulations were prepared by using plasticizer at 30% w/w of polymers weight in all the patches.

Table No.3: Composition of Allopurinol transdermal patches

S. No.	Code	Allopurinol (% w/w)	EC:PVP (Ratio)	Permeation Enhancer (% w/w)
1.	A1	20	4.5 : 0.5	-
2.	A 2	20	4 : 1	-
3.	A 3	20	2 : 1	-
4.	A 4	20	3:2	-
5.	A 5	20	2:3	-
6.	A D1	20	3:2	DMSO 2%
7.	A D2	20	3:2	DMSO 5%
8.	A D3	20	3:2	DMSO 10%
9.	A T1	20	3:2	Tween-80 2%
10.	A T2	20	3:2	Tween-80 5%
11.	A T3	20	3:2	Tween-80 10%
12.	A E1	20	3:2	Eucalyptus oil 2%
13.	A E2	20	3:2	Eucalyptus oil 5%
14.	A E3	20	3:2	Eucalyptus oil 10%
15.	A O1	20	3:2	Olive oil 2 %
16.	A O2	20	3:2	Olive oil 5 %
17.	A O3	20	3:2	Olive oil 10 %

Physiochemical Evaluation of Patches

The prepared transdermal patches were evaluated for their physiochemical characteristics like physical appearance, thickness, weight uniformity, drug contents, moisture contents, moisture uptake, flatness, tensile strength and pH. The results of physicochemical

characteristics are given in figures.

The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubble. The weight of transdermal patched varied from 164.37 to 172.01 mg which indicated that the prepared different batches of transdermal films were similar in weight. The thickness of different batches were found in range from 0.246 to 0.276 mm. A low standard deviation value in the film thickness measurement ensures the uniformity of formulated patches. No significant difference in drug content was observed in all the formulated patches which were found in range from 94.12 to 98.23%. The obtained results indicated that the method used for the preparation of transdermal patches was capable of possessing uniform drug content due to the homogenous dispersion of the drug.

The moisture content and moisture uptake of various formulations showed that with increasing in concentration of hydrophilic polymer (PVP) both percentages of moisture content and moisture uptakes were increases. The similar results have been reported by other researchers. The percentage of moisture contents and moisture uptake were found in the range from 1.64 ± 0.31 to 6.38 ± 1.04 and 2.43 ± 0.55 to 9.41 ± 0.75 respectively. The results indicated that the hydrophilicity of the polymers is directly proportional to the percent of moisture contents and moisture uptake. The low percentage of moisture content in formulations could help them to remain stable and prevents them from being completely dried. Also, low moisture uptake protects the material from microbial contamination and bulkiness of the patch (Valenta *et al*., 2005). Flatness studies were performed to determine the formulation construction. 100 % flatness of all the formulated patches indicated that there was no amount of constriction in formulated transdermal patches. Thus, formulated transdermal patches could better maintain a smooth surface when applied on to the skin.

Tensile strength of transdermal patches are important since they are expected to be sufficiently flexible and to have a mechanical strength on skin for a long period of time. Tensile strength results showed that strength of films were in a range from 0.346 to 0.438 kg/mm^2. The folding endurance determines the ability of patch to withstand rupture. It was measure manually and was found to be in the range from 34 to 48. The result indicated that the patches of all batches would not break and would maintain their integrity with general skin folding when used (Guy RH and Hadgraft J, 1987).

Dermatological product has an important role to be safe and non irritant. Formulations placed on the skin should possess a pH between 4 and 7 (Guy RH and Hadgraft J, 1987). The pH of film forming solutions was determined and it was observed in the range from 5.8 to 6.6.

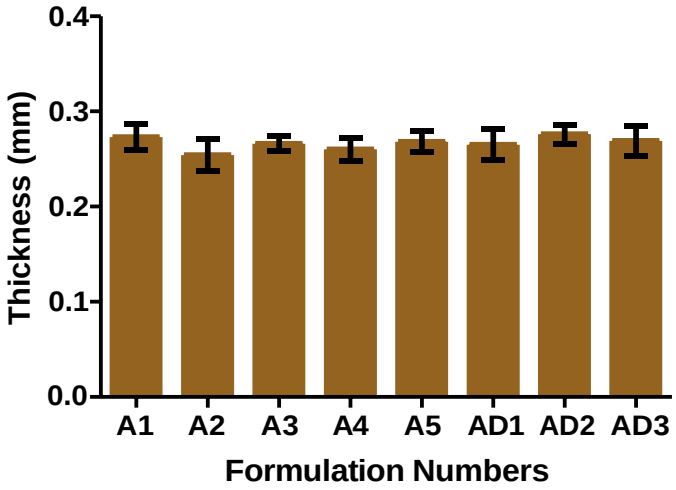

Figure No. 2: Measurment of Thickness of transdermal patches of different formulations

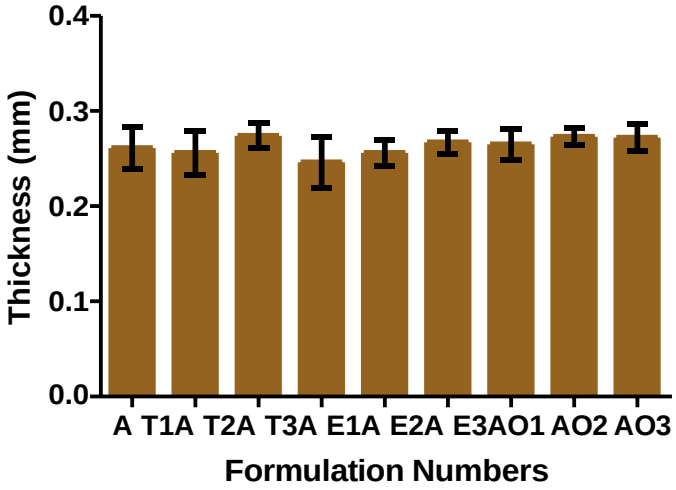

Figure No. 3: Measurment of Thickness of transdermal patches of different formulations

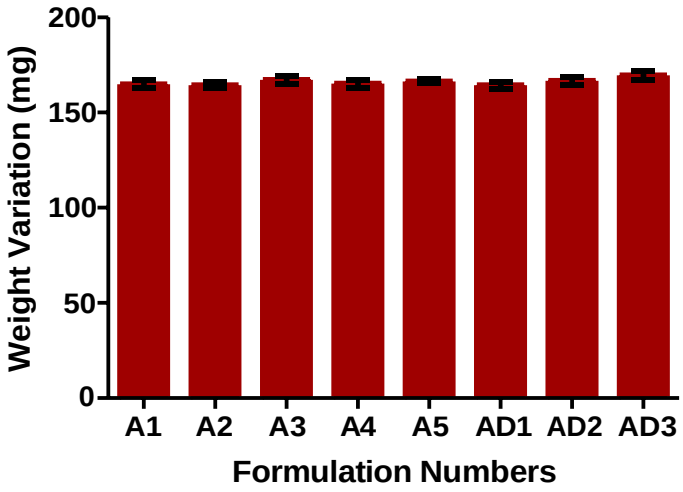

Figure No. 4: Weight variation of transdermal patches of different formulations

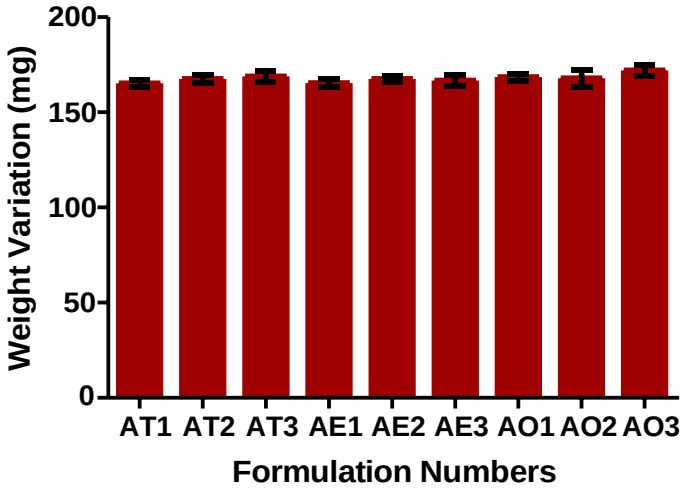

Figure No. 5: Weight variation of transdermal patches of different formulations

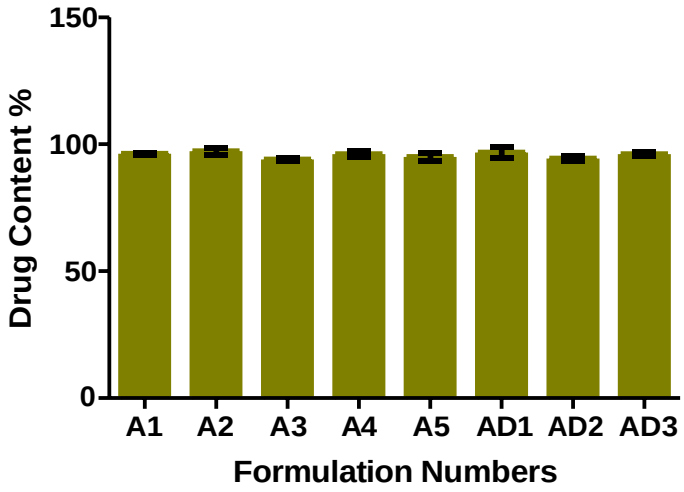

Figure No. 6: Drug Content percentage of transdermal patches of different formulations

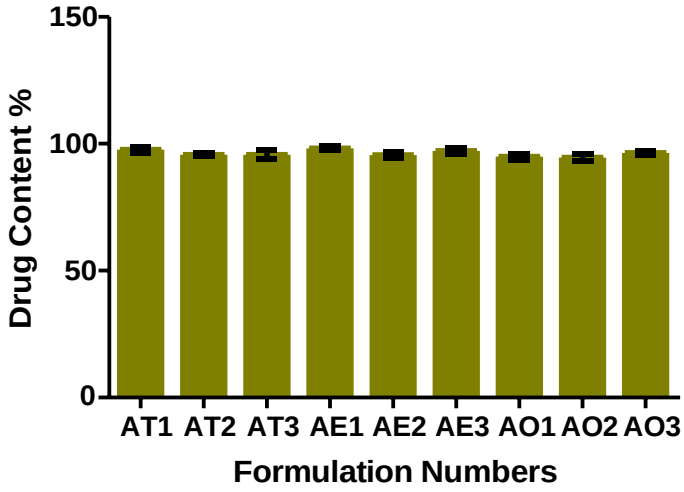

Figure No. 7: Drug Content percentage of transdermal patches of different formulations

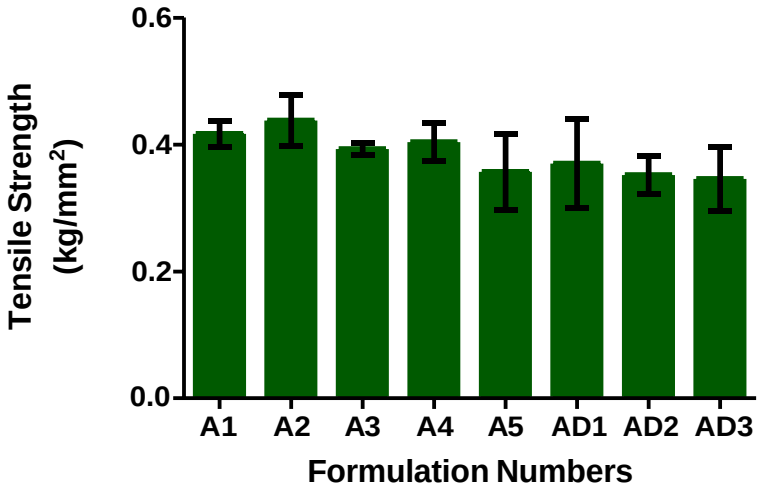

Figure No. 8: Tensile Strength of transdermal patches of different formulations

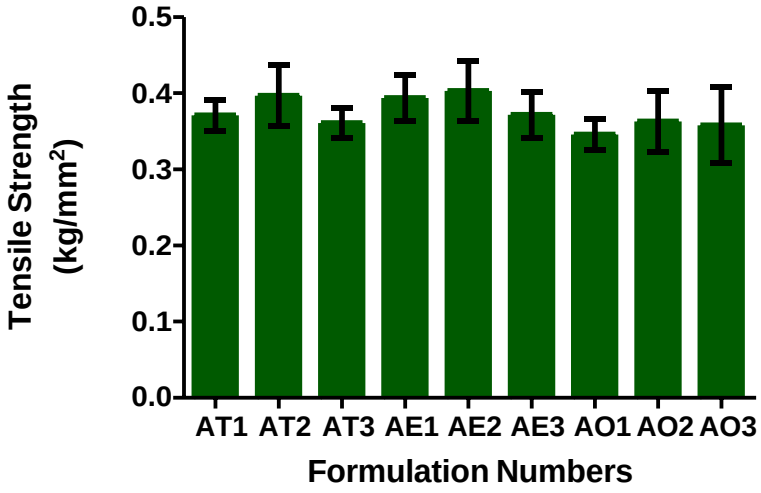

Figure No. 9: Tensile Strength of transdermal patches of different formulations

CONCLUSION

The objective of the present study was to develop transdermal matrix patch of allopurinol and assess its feasibility for transdermal application. Allopurinol is a anti-gout or Xanthine oxidase inhibitor agent used in the treatment of gout. Low dose maintenance therapy of Allopurinol has the capability to reduce potential side effects and improved patient compliance which are more common with conventional drug delivery.

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