



**Table 1: Formula of atenolol gel**

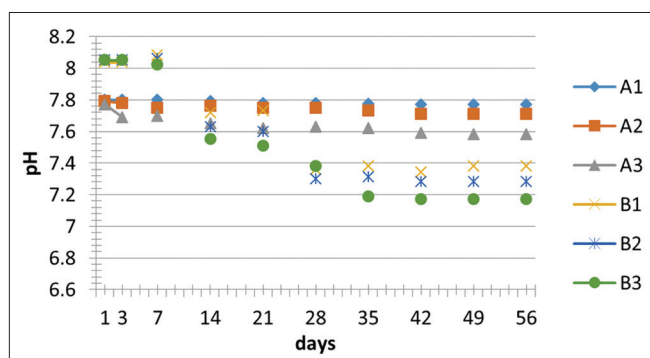
| Ingredients          | F <sub>A</sub>  |                 |                 | F <sub>B</sub>  |                 |                 |
|----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                      | F <sub>A1</sub> | F <sub>A2</sub> | F <sub>A3</sub> | F <sub>B1</sub> | F <sub>B2</sub> | F <sub>B3</sub> |
| HPMC (%)             | -               | -               | -               | 1.50            | 2.00            | 2.50            |
| Aqupec HV-505 (%)    | 0.50            | 1.00            | 1.50            | -               | -               | -               |
| Atenolol (%)         | 0.50            | 0.50            | 0.50            | 0.50            | 0.50            | 0.50            |
| TEA (%)              | 1.00            | 1.75            | 2.50            | 1.00            | 1.00            | 1.00            |
| Propylene glycol (%) | 25.00           | 25.00           | 25.00           | 25.00           | 25.00           | 25.00           |
| Ethyl acetate (%)    | 5.00            | 5.00            | 5.00            | 5.00            | 5.00            | 5.00            |
| DMDM hydantoin (%)   | 0.30            | 0.30            | 0.30            | 0.30            | 0.30            | 0.30            |
| Aquadest ad (%)      | 100.00          | 100.00          | 100.00          | 100.00          | 100.00          | 100.00          |

F<sub>A</sub>: Formula gel using Aqupec HV-505, F<sub>A1</sub>: Formula gel using Aqupec HV-505 0.5%, F<sub>A2</sub>: Formula gel using Aqupec HV-505 1%, F<sub>A3</sub>: Formula gel using Aqupec HV-505 1.5%, F<sub>B</sub>: Formula gel using HPMC, F<sub>B1</sub>: Formula gel using HPMC 1.5%, F<sub>B2</sub>: Formula gel using HPMC2%, F<sub>B3</sub>: Formula gel using HPMC 2.5. TEA: Triethanolamine

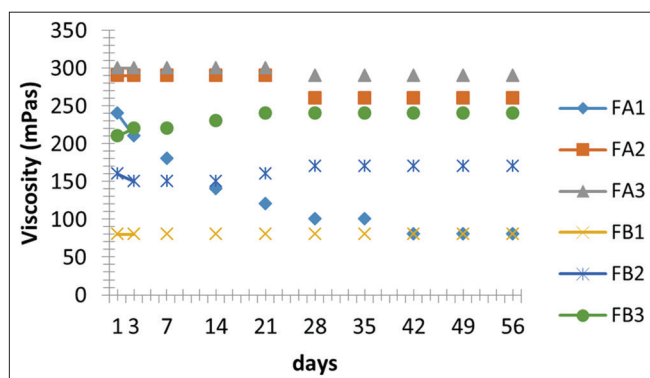
**Table 2: Formula of gel with various concentration of atenolol**

| Ingredients          | F <sub>A2.0</sub> | F <sub>A2.1</sub> | F <sub>A2.2</sub> | F <sub>A2.3</sub> |
|----------------------|-------------------|-------------------|-------------------|-------------------|
| Aqupec HV-505 1(%)   | 1.00              | 1.00              | 1.00              | 1.00              |
| Atenolol (%)         | -                 | 0.50              | 1.00              | 1.50              |
| TEA (%)              | 1.75              | 1.75              | 1.75              | 1.75              |
| Propylene glycol (%) | 25.00             | 25.00             | 25.00             | 25.00             |
| Ethyl acetate (%)    | 5.00              | 5.00              | 5.00              | 5.00              |
| DMDM hydantoin (%)   | 0.30              | 0.30              | 0.30              | 0.30              |
| Aquadest ad (%)      | 100.00            | 100.00            | 100.00            | 100.00            |

F<sub>A2.0</sub>: Formula of Aqupec HV-505 1% gel without atenolol, F<sub>A2.1</sub>: Formula of Aqupec HV-505 1% gel with atenolol 0.5%, F<sub>A2.2</sub>: Formula of Aqupec HV-505 1% gel with atenolol 1.0%, F<sub>A2.3</sub>: Formula of Aqupec HV-505 1% gel with atenolol 1.5%. TEA: Triethanolamine



**Fig. 1: pH of atenolol gels in various bases**



**Fig. 2: The viscosity of each gel during the time of storage**

**Qualitative and quantitative determination of atenolol in gel**

Qualitative analysis was performed by thin-layer chromatography

(TLC) into gel. Samples were dissolved in methanol and the eluent was ammonia:methanol (1:4). The spot was observed at UV light 254 nm.

Quantitative analysis was conducted by measuring the atenolol content in the sample. 1 g of gel was accurately weighed and placed in a 100 ml volumetric flask containing 30 ml of methanol, stirred for 30 min, and made up to volume. The amount of atenolol was calculated using standard obtained curve. The determination was conducted at 1<sup>st</sup> day and 56<sup>th</sup> day of preparation.

**Safety test**

The safety test was conducted into 10 volunteers using patch test method.

**RESULTS AND DISCUSSION**

**Physical stability investigation of atenolol in Aqupec HV-505 and HPMC bases**

Organoleptic investigation showed that all formulae have smooth texture, odorless, and spreadable. Gel with HPMC base was white opaque, while the one with Aqupec HV-505 was clear and transparent. The result was stable during 56 days of storage. Based on aesthetic considerations, Aqupec HV-505 1% was best one for gel base. So it is used for next experiment to which varying the Atenolol concentration in gels.

**pH of gels in various bases**

Ideal pH for topical preparation is 5.5–10. The result showed that pH of F<sub>A</sub> was 7.58–7.80, and it means that all gels with Aqupec HV-505 and HPMC base fulfilled the pH requirement. The pH was decreased during 56 days of storage, especially FB formulas, but they all still in required pH for topical preparation. pH of gels during storage is shown in Fig. 1.

**Viscosity of gels**

Investigation on gels' viscosity gave the results that viscosity was decreased during the time of storage (Fig. 2). A decrease in viscosity may due to indirectly monitor chemical degradation because changes at the molecular level may cause changes in viscosity [16-18].

Further investigation was conducted by varying the atenolol concentration on 1% Aqupec HV 505. Based on organoleptic investigation, almost all gels were also clear, transparent, and well spreadable. Aqupec HV-505 1.5% became turbid, especially, after 0.5% atenolol was added. No bleeding happened in all gels during 56 days of storage. Formula used in gels with various concentration of atenolol is shown in Table 2.

**Physical stability investigation of 1% Aqupec HV-505 gels with various concentration of atenolol**

*Organoleptic investigation*

Based on the result of organoleptic investigation including color, smell, and consistency during 56 days of storage, it was concluded that F<sub>A2.0'</sub>, F<sub>A2.1'</sub>, F<sub>A2.2'</sub>, and F<sub>A2.3</sub> had homogenous and stable during the time of investigation at ambient temperature. The results show that there were no visible changes in the gel formulation.

*pH of gel*

The pH of F<sub>A2</sub> was 7.74–8.30. Addition of atenolol causes an increase in pH. It may be caused by the physicochemical of Atenolol itself as weak base. The increase in the concentration of atenolol resulted in bigger pH value of gels. The pH of gels with various concentration of atenolol is shown in Fig. 3.

*Viscosity of gels*

The viscosity of gels containing atenolol was lower compared with those without atenolol, which is due to internal and molecular change of atenolol addition. Furthermore, the results revealed that the increase of atenolol concentration in gel formulation did not affect the viscosity. Effect of time of storage was investigated for 56 days. The results

AQ5

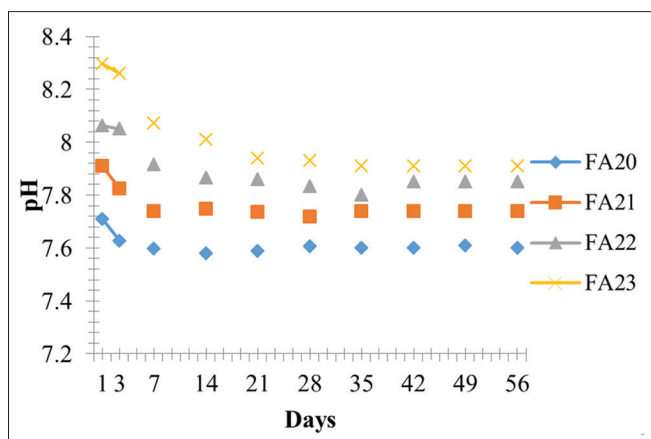


Fig. 3: pH of gels with various concentration of atenolol during the time of storage

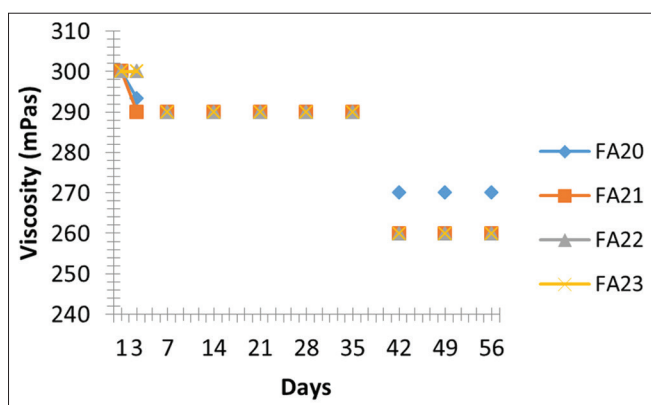


Fig. 4: Viscosity of gels with various concentration of atenolol during the time of storage

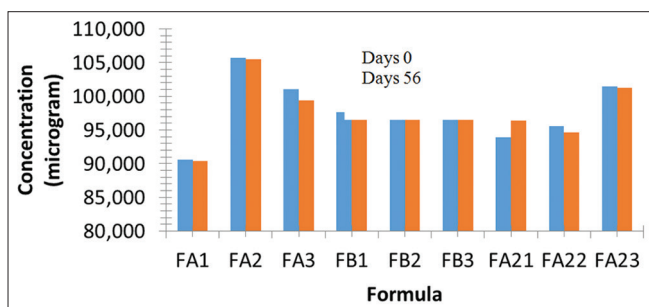


Fig. 5: Atenolol content in gels

Table 3: Qualitative analysis of atenolol after formulation and 56 days of storage

| Formula           | R <sub>f</sub> days of 0 | R <sub>f</sub> days of 56 |
|-------------------|--------------------------|---------------------------|
| Atenolol powder   | 0.8846                   | 0.8923                    |
| F <sub>A1</sub>   | 0.8925                   | 0.8923                    |
| F <sub>A2</sub>   | 0.8923                   | 0.9000                    |
| F <sub>A3</sub>   | 0.9000                   | 0.9000                    |
| F <sub>B1</sub>   | 0.8846                   | 0.8846                    |
| F <sub>B2</sub>   | 0.8923                   | 0.8923                    |
| F <sub>B3</sub>   | 0.8769                   | 0.9000                    |
| F <sub>A2.1</sub> | 0.8923                   | 0.8846                    |
| F <sub>A2.2</sub> | 0.8923                   | 0.8923                    |
| F <sub>A2.3</sub> | 0.9000                   | 0.8923                    |

showed that gel formulation was stable after 56 days of storage. Viscosity of gels with various concentration of atenolol during the time of storage is shown in Fig. 4.

**Microbial Investigation**

The test was conducted to prove that preservative used in formulation was effective. It was found that there was no bacterial growth after 14 days of investigation which can be concluded that the preservative is effectively worked in the gels.

**Qualitative analysis by TLC**

The purpose of the study was to investigate atenolol content in gels during the time of storage. First, the investigation was conducted by qualitative analysis using TLC method. Furthermore, the quantitative analysis was conducted to investigate the homogeneity content of atenolol in gel preparation. The study was performed into all gels at the day of preparation and after 56 days of storage. Qualitative analysis by TLC method showed that R<sub>f</sub> of atenolol in gels and atenolol powder as standard were unchanged after formulation, as well as after 56 days of storage as shown in Table 3.

**Quantitative analysis**

Atenolol content in gels is shown in Fig. 5. From the results, it can be concluded that drug content in gels did not significantly changed during the time of storage. Stability of atenolol in gel formulation can be explained by inert matrix using as gel basis. HPMC and Carbopol as matrix used in gel basis revealed the stability for atenolol after 56 days of storage.

**Safety test**

Safety test was conducted by Patch test method to find out whether the formulation may be caused or aggravated by a contact allergy to the skin. Positive reactions were observed; skin reaction nearly becomes red and/or itchy. The safety test gave the result that all gels were safe to be used because it did not give the allergic reaction to the volunteers.

**CONCLUSIONS**

Organoleptic investigation showed that all formulae have smooth texture, odorless, and spreadable. Gel with HPMC base was white opaque, while the one with Aqupec HV-505 were clear and transparent which was stable during 56 days of storage. Gels with Aqupec HV-505 and HPMC base were fulfilled the pH requirement for topical preparation. Viscosity of FA and FB was decreased during the time of storage. The addition of atenolol concentration did not affect the viscosity significantly.

**AUTHORS' CONTRIBUTIONS**

The entire author equally contributed to this work.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest.

**REFERENCES**

- Ghosh TK, Adir J, Xiang SL, Onyilofur S. Transdermal delivery of metoprolol. II: *In-vitro* skin permeation and bioavailability in hairless rats. J Pharm Sci 1995;84:158-60.
- Mohammed A, *et al.* Transdermal Delivery of  $\beta$ -blockers; 2006. Available from: <http://www.ingentaconnect.com>.
- Bhaskaran N, Harsha SN. Effect of permeation enhancer and iontophoresis on permeation of atenolol from transdermal gels. ??? 2000;62:424-6. AQ6
- Shinde UA, Modani SH, Singh KH. Design and development of repaglinide microemulsion gel for transdermal delivery. AAPS PharmSciTech 2018;19:315-25. AQ7
- Lionberger DR, Brennan MJ. Topical nonsteroidal anti-inflammatory drugs for the treatment of pain due to soft tissue injury: Diclofenac

- epolamine topical patch. *J Pain Res* 2010;3:223-33.
6. Deveda P, Jian N, Khambete H, Jain S. Gellified emulsion for sustain delivery of itraconazole for topical fungal diseases. *Int J Pharm Pharm Sci* 2010;2:10.
  7. El Laithy HM, El-Shaboury KM. The development of cutina lipogels and gel microemulsion for topical administration of fluconazole. *AAPS PharmSciTech* 2002;3:E35.
  8. Kumar L, Verma R. *In vitro* evaluation of topical gel prepared using natural polymer. *Int J Drug Deliv* 2010;2:58-63.
  9. Gennaro AR, editor. Remington: The Science and Practice of Pharmacy. 19<sup>th</sup> ed. Easton: Mack Publishing Company; 1995.
  10. Ansel HC, Allen LV Jr., Popovich NG. *Pharmaceutical Dosage forms and Drug Delivery Systems*. 7<sup>th</sup> ed. New York: Lippincott Williams and Wilkins; 1999.
  11. Aparna C, Srinivas KS, Patnaik R. Enhanced transdermal permeability of telmisartan by a novel nanoemulsion gel. *Int J Pharm Pharm Sci* 2015;7:335-42.
  12. Kim J, Shin SC. Controlled release of atenolol from the ethylene-vinyl acetate matrix. *Int J Pharm* 2004;273:23-7.
  13. Cho CW, Shin SC. Enhanced transdermal delivery of atenolol from the ethylene-vinyl acetate matrix. *Int J Pharm* 2004;287:67-71.
  14. Gupta SP, Jain SK. Development of matrix-membrane transdermal drug delivery system for atenolol. *Drug Deliv* 2004;11:281-6.
  15. Acharya A, Kumar GB, Ahmed MG, Paudel S. A novel approach to increase the bioavailability of candesartan cilexetil by proniosomal gel formulation: *In-vitro* and *in-vivo* evaluation. *Int J Pharm Pharm Sci* 2016;8:413-20.
  16. Souza C, de Freitas LAP, Maia Campos PMBG. Topical formulation containing beeswax-based nanoparticles improved *in vivo* skin barrier function. *AAPS PharmSciTech* 2017;18:2505-16.
  17. Wagemaker TA, Silva SA, Leonardi GR. Maia campos PMBG green *Coffea arabica* L. seed oil influences the stability and protective effects of topical formulations. *Ind Crop Prod* 2015;63:34-40.
  18. Tadros T. Application of rheology for assessment and prediction of the long-term physical stability of emulsions. *Adv Colloid Interface Sci* 2004;108-109:227-58.

#### Author Queries???

AQ1:Kindly check the edit made.

AQ2:Kindly review the sentence for more clarity.

AQ3:Kindly review the text part as it seems to be unclear.

AQ4:Kindly review the sentence as it seems to be incomplete.

AQ5:Kindly review the sentence.

AQ6:Kindly provide six author before et al

AQ7:Kindly provide journal name