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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF NOVEL FORMULATION'S FOR TOPICAL DELIVERY SYSTEM OF GLYCOPYRROLATE

Sujit A. Jadhav[1*], Dr. Anshu Sharma[1], Mayuresh Kothmire[1]

Bhupal Nobles' College of Pharmacy, Bhupal Noble's University, Udaipur (Rajasthan)

* Corresponding Author. E-mail: sujitpharma29@gmail.com

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ABSTRACT

Sweating is a physical and important process. The basic difference is made between two types of sweating: thermoregulatory and emotional sweat. Thermoregulation is essential to keep an even body temperature and for this reason homeostasis. Expanded sweating, as in hyperhidrosis, may additionally constitute an essential trouble. The ones affected revel in massive impairments in terms of the social and professional environments due to multiplied sweat production, and the ensuing subjective notion of illness on the person level can be giant. Topical drug delivery has emerged as an important delivery route over other routes of drug delivery as the merits of non-invasiveness, better patient compliance, especially when long-term treatment is required and pain-free self-administration for patients. Topical and systemic anticholinergic drugs like Glycopyrrolate continue to useful medications in the management of hyperhidrosis. They are the initial therapeutic options for all primary forms of excessive sweating. Most often topical administration means application to the body surface such as skin and mucous membrane to treat aliments via wide range of classes including topical solutions, creams, gels, ointments. Gels are a dosage form formed by entrapment of large amounts of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin.

INTRODUCTION

A new formulation and method for the delivery of active substances to human subjects as a quick drying film forming gel may overcome the problems of slow release, and of sensitization and irritation associated with transdermal topical patches**.** Efficient delivery through the skin (the film could occlude skin and thereby i) increase hydration, (ii) prevent loss of drug through sweating or from being rubbed off by contact with clothing or (iii) provide a local depot effect and create a more sustained concentration gradient or driving force); (iv) reduced dosing or application frequency for some of the same reasons; and (v) provide a barrier over sensitive skin. Sweat evaporation from the skin floor plays an important function in human thermoregulation and that is most apparent while the capability to sweat Is compromised in the course of periods of strenuous physical hard work and/or exposure to warm environments [1]. Hyperhidrosis is the abnormally excessive sweating that's not necessarily related to heat or exercise. Hyperhidrosis is a disorder characterized by excessive sweating which is required to control body temperature. The excessive sweating associated with the Hyperhidrosis can occur in the hands (Palmer Hyperhidrosis) in the armpits (Axillary Hyperhidrosis) or in the feet (Palmer Hyperhidrosis). Glycopyrrolate, like other anticholinergic (antimuscarinic) agents, inhibits the action of acetyl choline on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetyl choline but lack cholinergic innervation [2, 3]. The peripheral

cholinergic receptors are present in the autonomic effect or cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions.

2. MATERIAL AND METHOD

2.1 Material

Glycopyrrolate was received as a gift sample from the Harman Finochem, Aurangabad, Maharashtra, India. Other ingredients and solvents were obtained from different commercial suppliers.

2.2 Formulationof 1%Glycopyrrolate Topical Solution

Take 80% of batch size purified water. Add and dissolve Disodium EDTA under stirring. Add and dissolve Glycopyrrolate under stirring, stir for 20-30 min to dissolve completely or till get clear solution. Take Propylene glycol and heat to 50°C to 60°C, then add and dissolve Methyl paraben and Propyl paraben. Cool to below 30°C. Transfer mixture of propylene glycol, methyl paraben and propyl paraben into the above solution under stirring, stir for 15 min. Check and adjust pH to 6.5+- 0.2 using 10% Sodium Hydroxide solution. Make final volume with purified water and stir for 30 min.

2.3 Formulation of 1%Glycopyrrolate Gel

Take 50% batch size of purified water and dissolve Disodium EDTA in it under stirring. Add and disperse carbopol 980 in above step under stirring. Take 30% of batch size purified water in separate SS vessel and dissolve Glycopyrrolate in it under stirring. Transfer this solution to step i under stirring, stir for 20-30 min. Heat Propylene glycol to 50-60°C in Separate SS vessel and dissolve Methyl Paraben and Propyl paraben in it under stirring. Cool to below 30°C and transfer to step i under stirring. Check and adjust pH to 6.5 +-0.2 using 10% sodium hydroxide solution. Make up final weight using purified water and stir for 30 min.

3. EVALUATION

3.1 Drug-polymer compatibility study by FT-IR spectrophotometer: This was carried out to find out the compatibility between the drug and the polymer. About 1 mg of drug and 100 mg of KBr were taken in a mortar and pestle and triturated. A small amount of the triturated sample was taken into the DRS sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1}at resolution of 4 cm^{-1} and 15 scans per spectrum.

3.2 pH determination: pH measurements were carried out using a digital type pH meter (Pico, Lab India), by inserting the glass electrode completely into the solution and gel system resp. and waiting for stabilization of the pH.

3.3 Viscosity: The viscosity of the gels was measured using a Brookfield viscometer, at a controlled temperature of 30 ± 2˚C at 50 rpm.

3.4 Spreadability: Samples of gels were accurately weighed on a smooth flat surfaced glass plate. The initial diameter of the gel was noted. Another glass plate of same dimensions was placed on the first plate containing the formulation. Standard weight 300g was placed on the upper plate over the gel region for a period of 60 seconds. The weight and upper plate were gradually removed and final diameter of gel was measured.

3.5 Drug Content: Weigh accurately 10 mg of Glycopyrrolate and transfer to 100 mL volumetric flask. Add 75 mL of diluent, sonicate to dissolve it completely, make the volume up to the mark with diluent. The drug content was determined by a HPLC method using a C18 column and 1mL flow rate.

3.6 Diffusion study by Franz Diffusion Cell

Fresh skin was excised from the porcine ear region and adhering fat and other cartilage tissues were removed, the skin was used immediately after excising. It was sandwiched between the recipient and donor compartments of the Franz diffusion cells. Aliquots were withdrawn at specific time points and were inject into the HPLC for analysis of drug content.

3.7Stability study

The study consists of selected formulations of 1% Glycopyrrolate solution and 1% Glycopyrrolate gel were kept in environmental stability chamber maintained at 40 ºC ± 2 ºC/75% ± 5%RH for six months and samples were analyzed as duration of

Initial, 1, 3 and 6 months respectively for assay by using HPLC method.

4. RESULTS AND DISCUSSIONS

4.1 Drug-polymer compatibility study by FT-IR spectrophotometer

FT-IR spectroscopy study was carried out separately to check the compatibility of the drug and polymer used for the preparation of solution and gel. FT-IR was performed for the drug, polymer and final formulation. The spectrum obtained from FT-IR spectroscopy studies at wavelength from 4000 cm^{-1} to 400 cm^{-1} are shown in figure1, 2, 3, 4, 5, 6 and 7 and the characteristic peaks obtained are shown in table 3, 4 and 5.

4.2 pH: The pH of the topical solution and gel was found to be around 6.5 – 7.2. This can be considered to be the appropriate pH for topical application to the skin.

4.3 Viscosity: The apparent viscosity of the gels ranged between 900 – 1300cps. They were not highly viscous and easily flowable gels. This property is important because highly viscous and firm gels require rubbing onto the skin which generates friction

4.4 Spreadability: The spreadability of all gels was over 80 % as calculated from the formula. This can be attributed to the lower viscosity and flowability of the gels.

4.5 Drug Content: The drug content in the 1% Glycopyrrolate topical solution and 1% Glycopyrrolate gel ranged from 90% to 110%.

4.6 Diffusion Study: Drug diffusion through the porcine ear membrane was found to be very high indicating good permeation characteristics of the1% Glycopyrrolate solution and 1% Glycopyrrolategels as observed form the figures.

Table no.1:Formulation of 1%Glycopyrrolate Topical Solution

Sr. No	Excipient Name						
	Glycopyrrolate (gm)	Propylene Glycol (gm)	Methyl Paraben (gm)	Propyl Paraben (gm)	Disodium EDTA (gm)	NAOH (10% w/v)	Purified Water
1	1	5	0.25	0.1	0.1	Quantity sufficient to 6.5	Quantity sufficient upto 100 ml
2	1	2	-	0.2	-		
3	1	3	0.2	-	0.1		
4	1	5	0.18	0.02	0.1		
5	1	4	0.2	-	-		

Table no.2: Formulation of 1% Glycopyrrolate Gel

Sr. No	Excipient Name							
	Glycopyrrolate (gm)	**Propylene Glycol (gm)**	**Methyl Paraben (gm)**	**Propyl Paraben (gm)**	**Disodium EDTA (gm)**	**Carbapol 980 (gm)**	**NAOH (10% w/v)**	**Purified Water**
1	1	5	-	0.1	0.1	2	Quantity sufficient to 6.5	Quantity sufficient upto 100 ml
2	1	4	0.3	-	-	1		
3	1	5	0.25	0.02	-	3		
4	1	6	0.2	0.01	0.2	1		
5	1	5	0.18	0.02	0.1	1		

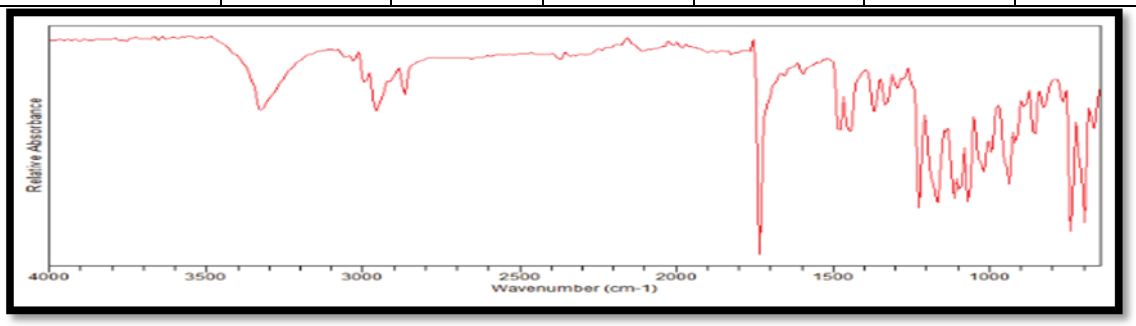

Fig no 1: IR Spectra of Glycopyrrolate

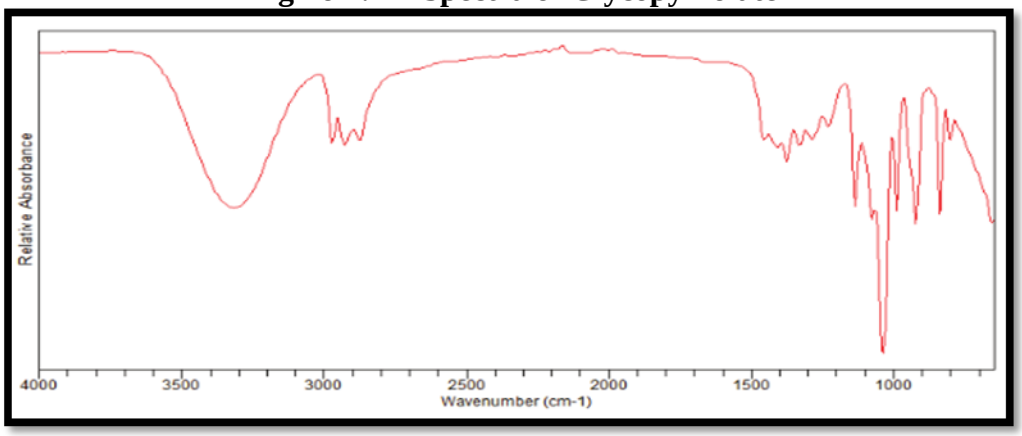

Fig no 2: IR Spectra of Propylene Glycol

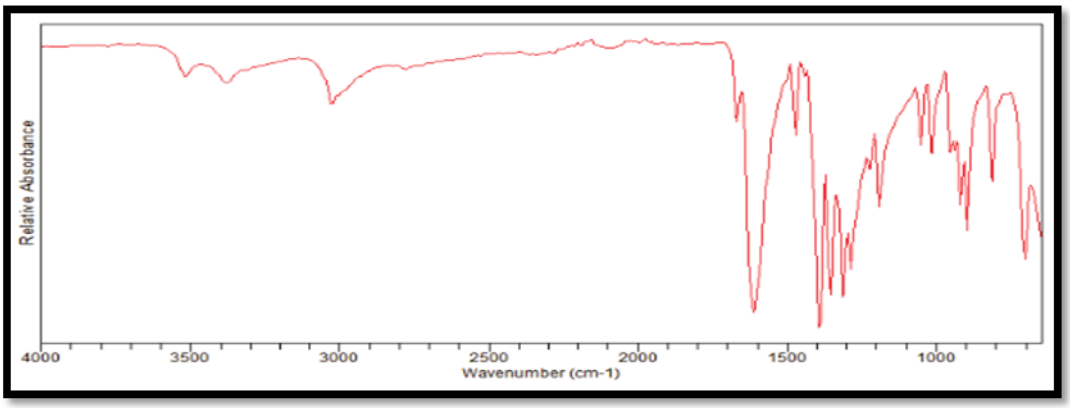

Fig no 3: IR Spectra of Disodium EDTA

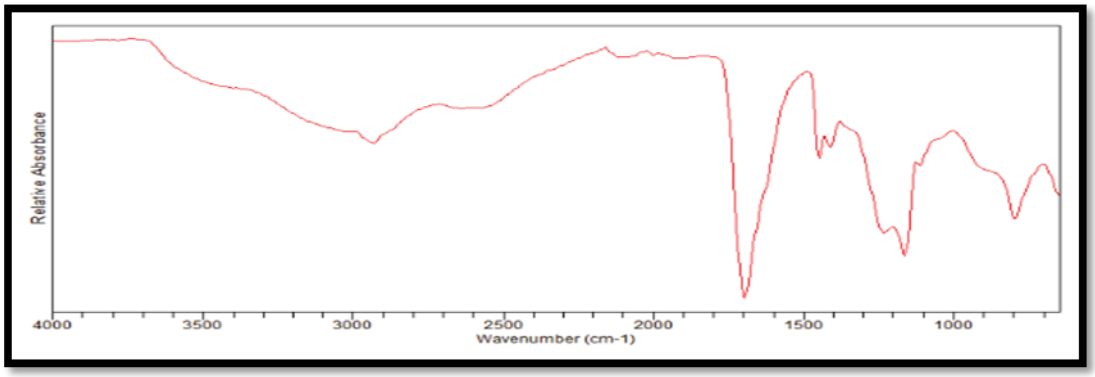

Fig no 4: IR Spectra of Carbapol 980

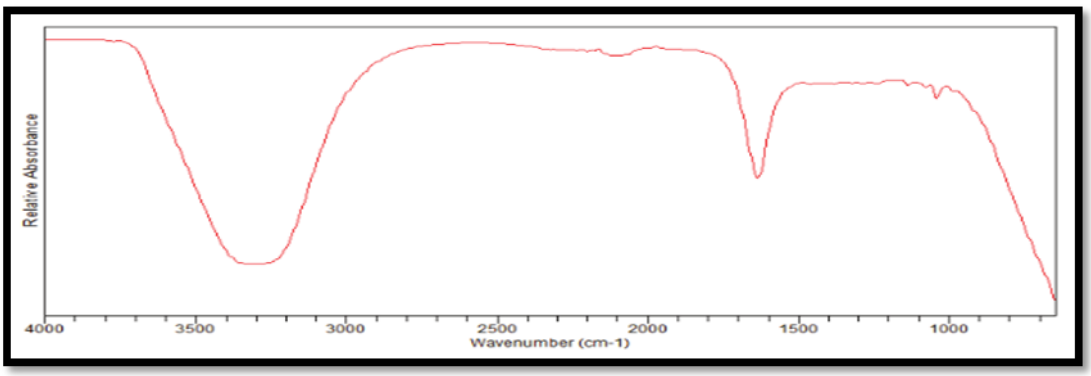

Fig no 5:IR Spectra of Glycopyrrolate 1% topical Solution

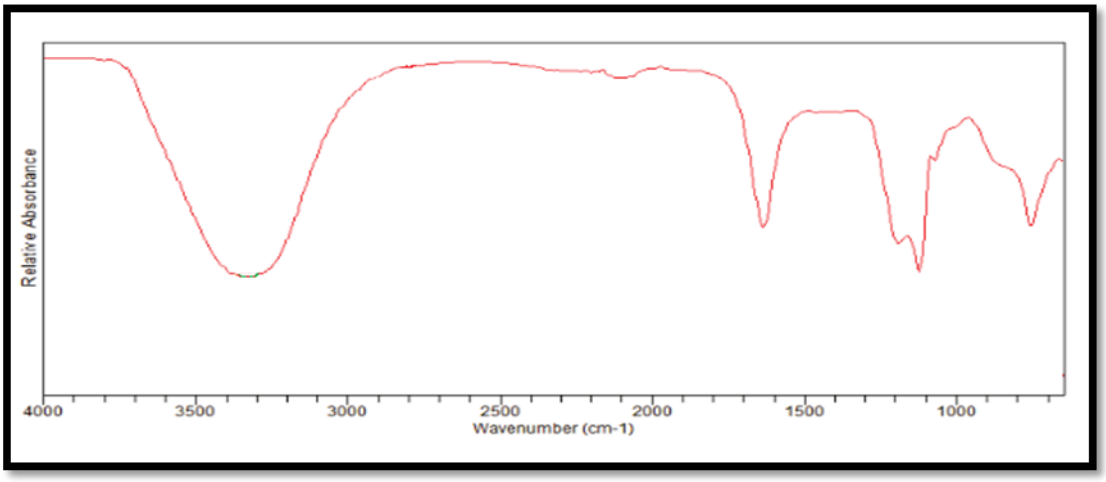

Fig no 6: IR Spectra of Glycopyrrolate 1% Gel

Table no 3: IR interpretation of API

Obtained peak value (cm^{-1})	Standard ranges of wave number (cm^{-1})	Bond	Characteristic functional group
3342.42	3400-3250	N-H(stretching)	Amine
1677.22	1760-1690	C = O(acid)	Alcohols, esters, carboxylic acid
930.11	950-910	O - H (Bending)	Alcohol
1650	1600-1700	C –H (Streching)	Alkane
1050	800-1200	C-C(Streching)	Aromatic

Table no4: IR interpretation of 1% Glycopyrrolate Solution

Obtained peak value (cm^{-1})	Standard ranges of wave number (cm^{-1})	Bond	Characteristic functional group
3351.32	3400-3250	N-H(stretching)	Amine
1679.42	1760-1690	C = O(acid)	Alcohols, esters, carboxylic acid
930.11	950-910	O - H (Bending)	Alcohol
1650	1600-1700	C –H (Streching)	Alkane
1052.43	800-1200	C-C(Streching)	Aromatic

Table no 5: IR interpretation of 1% Glycopyrrolate Gel

Obtained peak value (cm^{-1})	Standard ranges of wave number (cm^{-1})	Bond	Characteristic functional group
3351.32	3400-3250	N-H(stretching)	Amine
1679.42	1760-1690	C = O(acid)	Alcohols, esters, carboxylic acid
930.11	950-910	O - H (Bending)	Alcohol
1650	1600-1700	C –H (Streching)	Alkane
1052.43	800-1200	C-C(Streching)	Aromatic

4.7 Stability study

The results of effect of temperature and humidity at 40 ºC ± 2 ºC/75% ± 5%RH for 6 months in environmental stability chamber on selected formulation are shown in table. There was no significant change in 1% Glycopyrrolate solution and 1% Glycopyrrolate gel assay, the samples analyzed after 1, 3 and 6 months of storage & there was no significant change in percent assay after 6 months. Hence, from the below results, it can be concluded that the developed formulations were stable and retained their pharmaceutical properties over a period of 6 months.

Results are shown in following table

Table no.7: Stability observations forsix month

Time point in months	1% Solution		1% Gel		Acceptance criteria
	% Assay	% Absolute difference from initial assay value	% Assay	% Absolute difference from initial assay value	
Initial	99.00	NA	98.29	NA	**% Absolute difference from initial assay: NMT 5.0**
1	98.82	0.18	97.96	0.34	
3	98.05	0.96	98.21	0.08	
6	97.45	1.57	96.33	1.99	

5 CONCLUSIONS

In the present study, attempts were made to study the properties of 1% Glycopyrrolate solution and 1% Glycopyrrolate gel.In that study the trial no. 4 for topical solution and trial no. 5 for gel shows maximum good results. The possible drug and polymer interaction during the time of preparation was studied using FT-IR analysis. The result of FT-IR study revealed that there was no interaction between the selected drug and polymer. The diffusion study were also done for the finalized batch and found to be having good permeation characteristics. The final formulation was studied for effect of temperature and humidity in stability chamber for 6 months. The studies indicated that the formulations were stable and retained their pharmaceutical properties over period of 6 months.

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