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Formulation and evaluation of olmesartan medoxomil topical gel

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Abstract
The objective of the study is to formulate and evaluate aolmesartanmidoxomiltopical gel for their skin infections. Four gel formulations were prepared using gelling agents HPMC (F1-F2) and carbopol (F3-F4) and they were evaluated for physical appearance, drug content, viscosity, extrudability, pH, spreadability, *In vitro* diffusion profile. The formulated gel showed good physical characteristics. The formulation F2 (96.96%) show good drug content as the polymer concentration in them was higher. The spread ability of gel decreases with an increase in polymer concentration. The pH of the formulation was in the range of 6-8 which is considered acceptable to avoid the risk of irritation upon application to the skin. Among the formulations, F2 showed better release (97.24%) characteristics than other formulations. The stability study for the topical gel formulation was done as per ICH guidelines Formulated gels were homogenous, stable and complied with the guidelines.

Keywords: Olmesartanmidoxomil, Carbopol 934, FTIR Studies, Topical gel, *In vitro* drug release studies

Introduction
Topical gel formulations provide a suitable delivery system for drugs because 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 [1]. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed [2]. 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 then cream and ointment [3]. Olmesartanmedoxomil (OLM) is a potent first-line antihypertensive drug as it is a selective angiotensin II receptor blocker. It has few side effects such as tachycardia. OLM is classified as BCS class II. [4] OLM has low oral bioavailability (28.6%) due to having poor water solubility and oral problems such as the extensive hepatic first-pass effect and the efflux pumps in the gastrointestinal tract that interfere with the drug's absorption [5].

Materials
Olmesartan Midoxomil was obtained from Micro Lab, HYD. Carbopol 934 and HPMC were procured from Synpharma Research Labs, Hyderabad, and other chemicals the reagents used were of analytical grade.

Methodology
FTIR Studies [6]
Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of Drug, polymer and physical mixtures of samples were weighed and mixed properly to a uniform mixture. A small quantity of the powder was compressed into a thin semi-transparent pellet by applying pressure. The IR spectrum of the pellet from 400-4000cm^{1} was recorded taking air as the reference and compared to study any interference.

Formulation Development

Table 1: Formulation development of Topical gel

Ingredients	F1	F2	F3	F4
Drug	10	10	10	10
Carbopol934	100	200	-	-
HPMC	-	-	100	200
Glycerine	10	10	10	10
Methyl paraben	0.01	0.01	0.01	0.01
Water	Q.S	Q.S	Q.S	Q.S

Preparation of gels [7]

Gels were prepared by using different concentrations of drug, methyl paraben (preservative) and glycerine (plasticizer) and stored in cool place until further use.

Gel formulations were prepared by dispersing Carbopol, HPMC in water by continuous stirring for a period of 2 h. Drug was dissolved in propylene glycol or ethanol or isopropyl alcohol and the solution was added gently to HPMC and Carbopol under continuous stirring. The mixture was stirred gently with a spatula until homogeneous gel was formed. All the samples were allowed to equilibrate for at least 24 h at room temperature prior to performing rheological measurements

Characterization

Drug content [8]

Each formulation (1 g) was taken in a 50 mL volumetric flask and made up to volume with methanol and shaken well to dissolve the active constituents in methanol. The solution was filtered through What man filter paper and 0.1 mL of the filtrate was pipetted out and diluted to 10 mL with methanol. The content of active constituents was estimated spectrophotometrically by using standard curve plotted at 258 nm (λmax of active constituents in the Drugs)

pH measurement [9]

pH measurement of the gel was carried out using a digital pH meter by dipping the glass electrode completely into the gel system to cover the electrode. The measurement was carried out in triplicate and the average of the three readings was recorded.

Appearance and Homogeneity [10]

Physical appearance and homogeneity of the prepared gels were evaluated by visual perception. Viscosity [11]

Viscosity of gel was determined using Brookfield viscometer (S-62, model LVDV-E) at 25 o C with a spindle speed of the viscometer rotated at 12 rpm.

Spreadability [12]

Two sets of glass slides of standard dimensions were taken. The herbal gel formulation was placed over one of the slides. The other slide was placed on the top of the gel, such that the gel was sandwiched between the two slides in an area occupied by a distance of 7.5 cm along the slides. Hundred g weight of gel was placed on the upper slides so that the gel was between the two slides was pressed uniformly to form a thin layer. The weight was removed and the excess of gel adhering to the slides was scrapped off. The two slides in position were fixed to a stand without slightest disturbance and in such a way that only upper slides to slip off freely by the force of weight tied on it. A 20 g weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance of 7.5 cm and separated away from the lower slide under the influence of the weight was noted. The experiment was repeated for three times and the mean time was taken for calculation.

Spreadability was calculated by using the following formula:

$S = m \times l/t$

where,

S= spreadability, m-weight tied to upper slides (20 g),

l- length of the glass slide (7.5 cm), t- time taken in sec.

***In vitro* diffusion profile** [13]

In vitro release study of the formulated topical gel was carried out by using diffusion cell through membrane as a dialysis membrane. Diffusion cell with inner diameter 24mm was used for the study. 1 mL formulation was placed in donor compartment and Freshly prepared 7.4 phosphate buffer was placed in receptor compartment. Dialysis membrane was mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that the membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1mL of sample was withdrawn from receiver compartment after 1, 2, 3, 4, 5, 6, 7 & 8 hrs and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10mL in a volumetric flask with distilled water and analysed by UV spectrophotometer at 258 nm.

Stability studies [14]

The main objective of the stability testing is to provide evidence on how the quality of the drug product varies with time under the influence of temperature and humidity. The stability study for the topical gel formulation was done as per ICH guidelines in a stability chamber for a period of 3 months.

Results and Discussion

Drug - excipient compatibility studies (FT-IR)

Thecompatibility between the drug and these lected Olmesartan midoxomil and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-excipients mixture, which confirmed the absence of any chemical interaction between the drug, polymers and other chemicals.

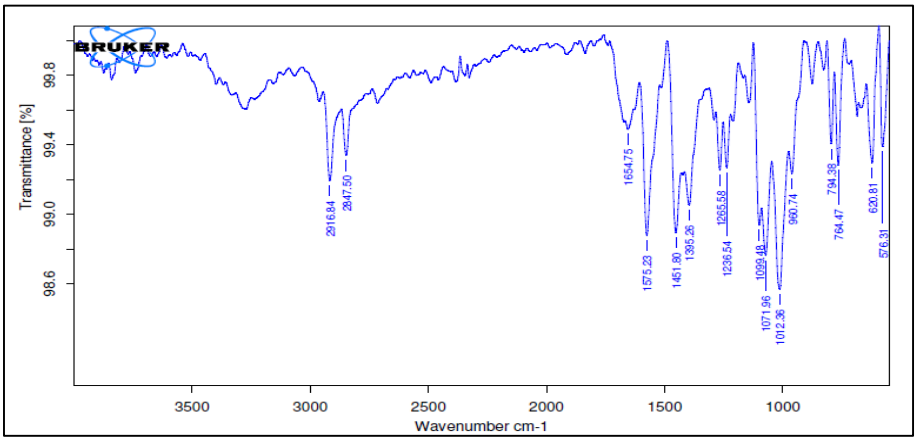

Fig 1: FTIR Studies of Olmesartanmidoxomil

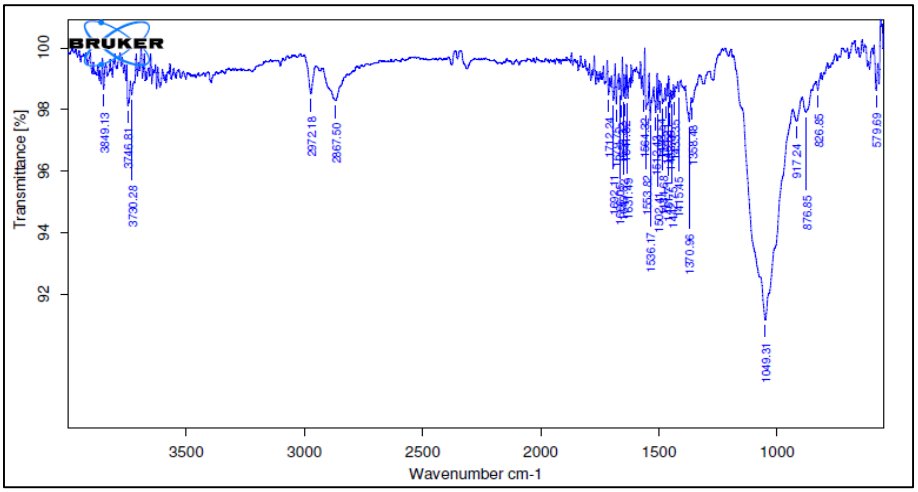

Fig 2: FTIR Studies of Optimized formulation

Evaluation of Gel formulation

pH value

The pH values of all the formulations were in the close range of neutral pH (7.1 -7.8) which is considered acceptable to avoid the risk of irritation upon application to the skin.

Viscosity

Polymers were included in the designed topical formulations in order to provide a prompt release of drug and to achieve as well as to maintain the drug concentration within the therapeutically effective range. As the concentration of the polymer was fixed as 1.5% in all the gel formulations no variation in viscosity was observed. Further the value between 0.36 and 0.38 poise was reported to be an ideal viscosity value for topical gel formulation developed using carbopol polymers.

Spread ability

Values of the spreadability indicated that the gel formulations are easily spreadable. Among the gel formulations F1 to F4, more than 90% of the contents were extrudable indicating they have excellent extrudability

Drug content

Maximum drug content discovered in the F1& F4 batch (94.38% to 96.96%) respectively. All the formulations were in the limits (90-110)%.

***In vitro* drug release profiles**

The *In vitro* release profiles of all the 4 formulations made using carbopol elicited almost 90% release from the formulation within 8 h.

Table 2: Physicochemical evaluation of Olmesartanmidoxomil gel

Formulation code	pH	Viscosity	Spreadability Gcm/sec	Drug content (%)
F1	7.3	0.36	37.86	95.80
F2	7.8	0.35	40.27	96.96
F3	7.1	0.40	39.46	94.47
F4	7.5	0.37	41.89	94.38

***In vitro* release study**

Phosphate buffer pH 7.4 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of Olmesartanmidoxomil patches containing different ratios of synthetic polymer. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table 3: *In vitro* drug release profiles of Olmesartanmidoxomil

Time	F1	F2	F3	F4
0	0	0	0	0
1	18.90	20.20	23.27	22.30
2	24.56	37.52	34.96	37.46
3	38.91	45.24	48.53	47.22
4	45.73	53.93	57.25	54.78
5	57.93	64.24	67.24	64.10
6	72.72	71.51	76.52	71.93
7	82.25	83.46	84.90	82.50
8	95.20	97.24	96.25	93.46

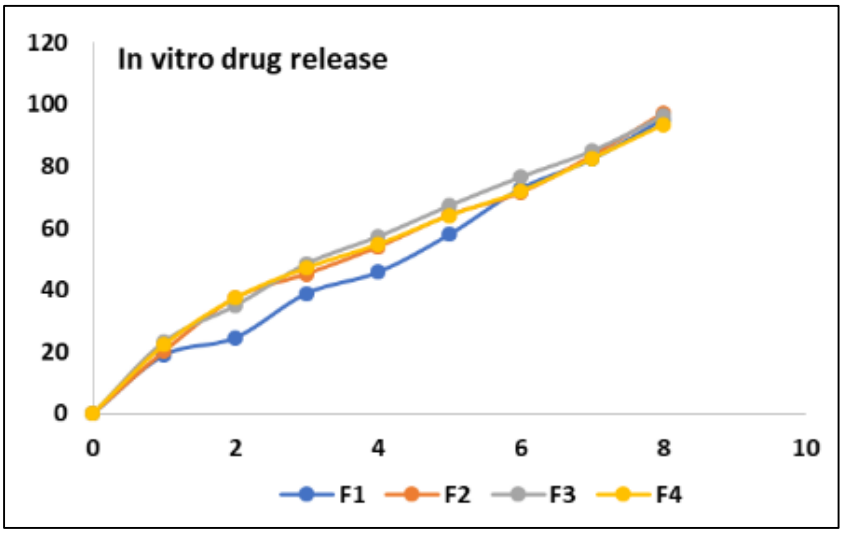

Fig 3: Drug release for (F1-F4) formulations

Stability studies

Table 4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Physical appearance	Drug content	% Cumulative drug release
0	No change in color	96.96	97.24
90	Slight yellowish color	96.52	96.50

Conclusion

From above results, we can conclude that Olmesartanmidoxomil gel formulations prepared with different gelling agents: sodium alginate and Carbopol934 showed acceptable physical properties and drug release study. All prepared gel showed acceptable physical properties concerning color, spread ability and pH value. Among all gel formulations, carbopol gels shows superior drug release after that sodium alginate shows decreasing order of drug release. In carbopol gel formulations, thedrug release was decrease with increase in carbopol concentration because polymer concentration increases, viscosity increases. Viscosity is negatively related to the release of active substance (Olmesartanmidoxomil) from formulations. Stability studies in all gel formulations showed that, the physical appearance, drug content and drug release in all gel formulations remain unchanged upon storage for 3 months.

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