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Development Characterization and Evaluation of Ointment containing Crisaborole using Co-solvency Method

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Abstract

Crisaborole has broad-spectrum anti-inflammatory activity by mainly targeting phosphodiesterase 4 (PDE4) enzyme that is a key regulator of inflammatory cytokine production. As this enzyme is expressed in keratinocytes and immune cells, crisaborole mediates an anti-inflammatory effect on almost all inflammatory cells. Topical application of this drug is useful as it potentiates the localization of this drug in the skin and this anti-inflammatory activity is in the low micromolar range. The objective of present research work is to enhance the aqueous solubility of poorly water soluble drug Crisaborole using Co-solvency technique. The prepared formulation was evaluated for physical characteristics, drug content and drug release.

Keywords: Crisaborole, Ointment, Co-solvency

Introduction

Crisaborole has broad-spectrum anti-inflammatory activity by mainly targeting phosphodiesterase 4 (PDE4) enzyme that is a key regulator of inflammatory cytokine production. As this enzyme is expressed in keratinocytes and immune cells, crisaborole mediates an anti-inflammatory effect on almost all inflammatory cells. Topical application of this drug is useful as it potentiates the localization of this drug in the skin and this anti-inflammatory activity is in the low micromolar range. It belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility 0.0234 mg/ml. Hence it is necessary to increase the solubility of drug in order to improve to increase bioavailability to show effective pharmacological action. The drug is having poor aqueous solubility 0.0234 mg/ml.Crisaborole is an efficacious drug in the management of skin disease and psoriasis. But the major drawback is its poor aqueous solubility.

Moreover, recent studies evidenced its efficacy in patients with skin disease and psoriasis. But it's very low aqueous solubility and poor dissolution can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action. Therefore, improvements in solubility and/or dissolution rate of Crisaborole may be achieved through the preparation of Co-solvency technique.

Different solubility enhancement techniques have been developed till present out, nowadays researchers are mainly focusing on novel solubility enhancement technique to improve solubility of drug.

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Bioavailability of oral preparation is highly depending on the solubility. Co-solvency is a novel and most important method to increase solubility of water insoluble solid drug (BCS Class II) for formulation of semi-solid dosage form. It can enhance dissolution rate as well as bioavailability of drug.Rapid release rate can be obtained and this can be efficiently used for water insoluble/poorly water soluble drugs.[1-3]

The objective of present research work is to enhance the aqueous solubility of poorly water soluble drug Crisaborole using Co-solvency technique.

Material and Methods

Formulation of Crisaborole ointment 2% by using co solvents

Initially ointment will be prepared by melting hard paraffin at 70ºC. Heat the propylene glycol at 70ºC and added in melted paraffin wax under stirring. Drug mixture was prepared by dissolving the drug in PEG in another vessel. Then Drug mixture was added in melted wax base under stirring. The entire mixture will be stirred while cooling to form Crisaborole ointment. Various compositions of the ointments were prepared for evaluation. [4-6]

Evaluation of optimized ointment formulations [4-6]

Physical Examination:

The prepared ointment formulations were inspected visually for their color, odor, Appearance.

Determination of pH of ointment formulation

Approx. 20g of sample was taken in glass beaker. Dip the pH sensor arm in the sample then Record the reading when reading was stabilized.The determinations were carried out in triplicate and average of tree readings were note.

Rheological Properties

Viscosity: The viscosity was determined by using Brookfield viscometer.

preadability

Spreadability of the formulation was determined by an apparatus, which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pully at one end. A rectangular ground glass plate (20cm x 20cm) was fixed on the block.

Determination of saturation solubility of ointment formulations

Solubility study was performed according to method reported by Higuchi and Connors. The various F1,F2,F3,F4,F5,F6 were added in 10 ml distilled water taken in stoppered conical flask and were shaken for 24 hrs at $37^0C \pm 1$ in orbital shaker. Two ml aliquots were withdrawn at 1 hr intervals and filtered. The filtered solutionwasanalyzed spectrophotometrically at 250 nm against blank.

Drug content

The ointment formulation equivalent to unit dose of drug was weighed accurately and dissolved in 100 ml of phosphate buffer 7.4 and filtered. The solutions were analyzed by UV spectrophotometer at 250 nm and drug content calculated accordingly.

In vitro Drug Release Studies

In vitro drug release studies of samples were carried out by using Franz diffusion cell. Dialysis membrane previously soaked in pH 7.4 phosphate buffer was taken and placed in between donor and receptor compartments. In the donor compartment 1gm of formulation was added. Volume of the diffusion medium was maintained 25 ml in receptor compartment and temperature maintained at 34 ± 0.5°C, and rpm was maintained at 25 by using hot plate magnetic stirrer. Aliquots were withdrawn at intervals of 30, 60, 120 min…..up to 6hours and replaced by equal volumes of diffusion medium. Aliquots were suitably diluted with pH 7.4 and analyzed by UV Spectrophotometer at 250 nm. F6 shows 98% of drug release within 6 hours..

Results and Discussion

The prepared formulation was evaluated for physical parameters. The pH of all the formulations is found in the range of 5.4 to 6.4. The viscosity of all the formulations were found the range of 25900 to 28996, which was similar as given in the reference. The spreadability was found in the range of 31 to 36 which was found to be similar as given as given in the reference. Saturation solubility studies were carried out for pure drug, as well as for prepared ointment formulations. From the result of saturation solubility studies it was observed that there was an increase in solubility of drug in formulations as compared to pure drug.

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Table 1: Composition of Crisaborole Ointment 2%

Formulation Code	Crisaborole (drug)	Co solvent(PEG400) (g)	Co solvent Propylene glycol (g)	Petrolatum (Paraffin wax)
F1	2 g	4	4	Upto 100 g
F2	2 g	6	4	Upto 100 g
F3	2 g	4	5	Upto 100 g
F4	2 g	6	5	Upto 100 g
F5	2 g	4	6	Upto 100 g
F6	2 g	6	6	Upto 100 g

With increase in the concentration of cosolvents solubility of drug increased and the ointment formulation containing high concentration of propylene glycol and PEG 400 in (F5) and (F6) has increased the solubility up to five times. This improves its wettability resulting in a significant increase in solubility. The drug content estimation was performed to ensure uniform distribution of drug. The drug content of crisaborole ointment 2% was performed for all the prepared formulations. The result indicates that the drug content in all the formulations was found uniform between 89% to 97% which was scanned spectrophotometrically at λmax 250 nm. Formulated ointment preparations of crisaborole showed a significant increase in the drug releases compared with pure crisaborole. In the formulations F1 and F2 showing 92.3% and 91.4% drug release, F3 and F4 showing 93.4% and 93.7% drug release, and F5 and F6 showing 96.4% and 97.6% drug release respectively. All the formulation shows improved drug release rate as compared to pure crisaborole.

Table 2: Evaluation Parameters of prepared formulation

Batch code	Color	Odor	Appearance	pH	Viscosity (cps)	Spreadability (g.cm/sec)	% Drug content
F1	White off	Odorless	Excellent	6.1	26800	31	92%
F2	White off	Odorless	Excellent	5.6	25900	33	90%
F3	White off	Odorless	Excellent	6.0	24600	34	89%
F4	White off	Odorless	Excellent	5.4	28010	36	97%
F5	White off	Odorless	Excellent	6.4	28996	35	96%
F6	White off	Odorless	Excellent	6.5	27600	34	92%

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Table 3: Saturation solubility study of various formulation

Formulation Code	Saturation Solubility (µg/ml) at 37^0 C in water	Percentage Solubility Enhancement%
Pure crisaborole	0.021	-
F1	0.043	20%
F2	0.045	21%
F3	0.052	24%
F4	0.058	27%
F5	0.061	29%
F6	0.063	30%

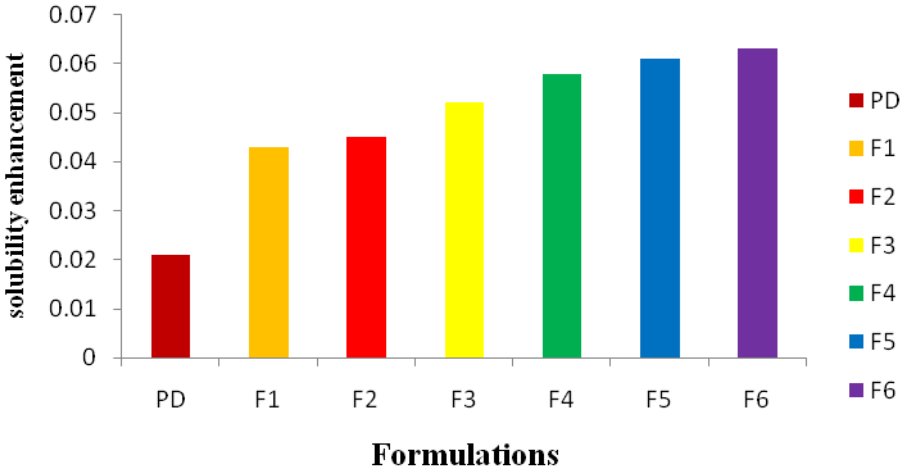

Fig. 1: Solubility graph of batches F1 to F6

Table 4: In- vitro release crisaborole ointment of 2% formulation F1-F6

Time (min)	Drug	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
30	7.07	15.2	14.5	16.4	16.2	18.4	19.1
60	15.1	31.5	30.2	32.2	31.2	35.2	37.2

120	26.8	64.3	62.1	64.5	63.7	67.4	68.5
180	36.19	77.5	76.3	79.5	78.5	80.5	82.5
240	41.01	84.3	82.5	86.3	85.3	88.3	89.3
300	45.11	90.7	89.8	91.3	92.4	93.3	94.3
360	48.21	92.3	91.4	93.4	93.7	96.4	97.6

Conclusion

The prepared ointment formulations were inspected visually for their color, odor, Appearance. The colors of all the ointments was found as white and white off. All the formulations are odor less and all the formulations were found to be excellent to good in appearance. The pH of all the formulations is found in the range of 5.4 to 6.5, which are found to be similar as given in the reference. The viscosity of all the formulations was found the range of 25900 to 28996, which was similar as given in the reference. The spreadability was found in the range of 31 to 36 which was found to be similar as given as given in the reference.

Saturation solubility studies were carried out for pure drug, as well as for prepared ointments. From the result of saturation solubility studies it was observed that there was an increase in solubility of drug in ointment formulations as compared to pure drug. With increase in the concentration of co-solvents solubility of drug increased and the ointment containing propylene glycol and polyethylene glycolin (F5) and (F6) has increased the solubility up to five times. This improves its wettability resulting in a significant increase in solubility. The drug content estimation was performed to ensure uniform distribution of drug. The drug content of crisaborole ointment 2% was performed for all the prepared formulations. The result indicates that the drug content in all the formulations was found uniform between 89% to 97% which was scanned spectrophotometrically atλ max 250 nm.

The in vitro drug release profile of pure drug Crisaborole, formulated ointment preparations in dissolution medium are shown in figure (6.3.9, 6.3.10, 6.3.11). Formulated ointment preparations of crisaborole showed a significant increase in the drug releases compared with pure crisaborole. In the formulations F1 and F2 showing 92.3% and 91.4% drug release, F3 and F4 showing 93.4% and 93.7% drug release, and F5 and F6 showing 96.4% and 97.6% drug release respectively. All the formulation shows improved drug release rate as compared to pure crisaborole.

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