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Formulation and Development of Transdermal Spray of Ibandronate Sodium

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ABSTRACT

Osteoporosis is a major disorders in the current scenario. Various therapies are available but from that Ibandronate Sodium is one of the newer anti-osteoporotic agents. This drug has certain drawbacks Low Bioavailibity, GI complication, Painful or Burning Urination, esophagus irritation. In the present investigation, an attempt has been made to enhance the Permeation and decreasing side effect, thereby increasing bioavailability and improved patient compliance by developing transdermal spray of Ibandronate Sodium. Preliminary trials were carried out for a selection of polymer and permeation enhancer. PVP K-30 and Camphor: Menthol were selected as polymer and permeation enhancer in a concentration of 5%, 10% and 4%, 6 %. 2^3 full factorial design was used to study the effect of the independent variable on the dependent variable (% CDR at 24 hr, Drying Time, Viscosity). Formulation batch B1, B2,...B8 were prepared. Parameters were carried out along with compatibility studies and in vitro drug release studies. From this study, B8 batch was selected which give drug release (83.38%) up to 24 hr. Final formulation follows Higuchi release kinetics.

INTRODUCTION

Ibandronate sodium used for the treatment of osteoporosis. Ibandronate Sodium has anti-resorptive activity and little effect on another organ system. They act on bone by binding to hydroxyapatite and by inhibiting activation of osteoclasts. The major drawbacks of Ibandronate Sodium have low bioavailability, esophagus irritation, Gastrointestinal problem, and painful or burning urination to overcome this type of problems, it is necessary to prepare Transdermal drug delivery formulation. In this study, different polymer and permeation Enhancer used for this purpose, Poly Vinyl Pyrrolidone K- 30 and Eutectic Mixture of Camphor: Menthol (1:1) has been used to the transdermal spray of different active materials.

MATERIALS AND METHODS

Materials

Ibandronate Sodium (Sai Moreshwar Healthcare, Vadodara), Poly Vinyl Pyrrolidone K30 (PVP K 30), Camphor, Menthol, Propylene Glycol, Iso Propyl Alcohol (IPA).

Methods

(a) Preparation of polymeric solution [2,3,10,13]

Adding film-forming polymer like PVP K-30 to 10 ml solvent system of IPA and Water (8:2 ml). The polymer was allowed to dissolve for 2 hours placed on digital magnetic stirrer maintained at speed 300 rpm. After complete solubilization of the polymer, plasticizer was added into the above mixture, PG was used as a plasticizer. A mixture of permeation enhancer (Camphor: Menthol, 1:1) was added to the above solution under constant stirring. The polymeric solution was preserved and stored in the refrigerator in glass bottles before crimping in a spray bottle.

(b) Preparation of Transdermal Spray [11,12]

The 20 ml polymeric solution of the optimized batch was filled into the cylindrical aluminum spray container having 40 ml volume capacity. Then crimping was done with a machine. And finally 12 ml hydrocarbon gas as a propellant was filled into the spray container in an upright position.

Evaluation

a) Viscosity [5,8,14]

The viscosity of the solution was measured by using Brookfield viscometer (Brookfield Engineering. La. Inc.MA, USA). The LVT spindle was rotated at 50 rpm. The result of viscosity is shown in Table 2.

b) Drying Time [12,14,15]

Evaporation time is the time required for the spray film to dry and it was estimated by spraying the formulation on a glass substrate and noting down the drying time. The results of the drying time are shown in Table 2.

c) *In-vitro* drug release study [12,14]

Cellulose membrane was used for the Drug Release study using Franz diffusion cell. The receptor compartment was filled 20 ml of a phosphate buffer P^H 7.4. Then, 1 ml of polymeric solution was filled into a donor compartment.

3 ml of aliquots were withdrawn periodically at a suitable time interval from the compartment. Fresh Phosphate Buffer P^H 7.4 was replaced to the receptor compartment and sample was analyzed by UV Spectrophotomatically at 265 nm against the blank solution. Three replicates of each experiment were performed. The results of *in-vitro* drug release are shown in Table 2.

d) pH of formulation [12, 14]

pH of the solution was measured using a P^H meter. The polymeric solution was kept in beaker up to a suitable level and an electrode was dipped in the solution and a digital scale on P^H meter which indicates the P^H of the solution was recorded.

e) *Ex-vivo* skin permeation study [12,14]

Drug permeation through excised rat skin was studied for 24 h using Franz diffusion cells. Hair was carefully removed from the abdominal region and the skin was made by an excision. The skin of the dermal side was completely cleaned of any adhering tissues. The skin of the dermis part was clean 3 to 4 times with a wet cotton swab soaked in iso-

propanolol to remove any adhering fat material. The skin specimens were cut into appropriate size after carefully removing subcutaneous fat and washing with normal saline. The skin was mounted in a Franz diffusion cell, kept at 37 ^{0}C. The receptor compartment was filled 20 ml of phosphate buffer P^H 7.4 to ensure sink condition were kept at 37 ± 0.5℃. Uniform mixing of the receptor medium was provided by magnetic stirring. The spray preparation was applied at an amount equivalent to 1 % w/v Ibandronate Sodium on the membrane in the donor compartment ensuring an intimate contact with the rat skin. 2 ml of aliquots were withdrawn periodically at 1, 2, 3, 4....8 hour from the sampling arm of the receptor chamber. Fresh diffusion media were replaced at the same time in the receptor chamber. The samples were analyzed by UV Spectrophotometrically at 265 nm against the blank solution. Three replicates of each experiment were performed. The results of in vitro drug release are shown in Table 2.

f) Spray Pattern [12,14]

Spray pattern checked by delivering on white paper. The result of a spray pattern is shown in Figure 6.

g) Spray angle [12,14]

In this method of impingement of spray on a piece of paper. Methylene Blue (10mg) was dissolved in the formulation to facilitate visualization. The sprays are actuated in horizontal direction onto a white paper mounted at a distance of 15 cm from the nozzle. The radius of the circle, formed on the paper, was recorded. Spray angle is calculated from the following equation:

$$\text{Spray angle} = \tan^{-1}(l/r)$$

Where l is a distance of paper from the nozzle & r is the radius of the circle.

The results of the spray angle are shown in Figure 6.

h) Content per Spray [12,15]

It was determined by the dispersing the spray solution into the beaker of phosphate buffer P^H 7.4 solution by a single actuation of the spray. Then the resulting solution was tested spectrophotometrically at 265. The amount of drug was measured from the calibration curve.

i) Skin irritation study [12,15]

The optimized formulation was sprayed on the dorsal skin of healthy rat and resulting reaction such as Irritation, inflammation, erythema, and edema were inquired after 24 h. The results of skin irritation study are shown in Figure 7.

RESULTS AND DISCUSSION

Table No. 1: Formulation ingredients for the formulation of transdermal spray

Batch	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8
Ibandronate Sodium (mg)	150	150	150	150	150	150	150	150
PVP K-30 (mg)	50	100	100	100	100	50	50	50
IPA: Water (ml)	8:2	8:2	8:2	8:2	8:2	8:2	8:2	8:2
Camphor :Menthol (mg)	2:2	2:2	3:3	2:2	3:3	2:2	3:3	3:3
Propylene Glycol (ml)	1	0.5	1	1	0.5	0.5	1	0.5

Table No. 2: Evaluation of a prepared batch of transdermal spray

Batch code	%CDR	Drying Time	Viscosity
B-1	82.32	48.23	89.54
B-2	76.32	50.23	64.65
B-3	78.37	48.21	70.74
B-4	72.71	61.22	56.35
B-5	79.96	89	65.93
B-6	82.48	47.12	55.24
B-7	77.90	51.34	75.46
B-8	83.38	44.78	38.54

Table No. 3: Comparison of Drug Release Profile of Optimized Batch and Pure Drug Solution

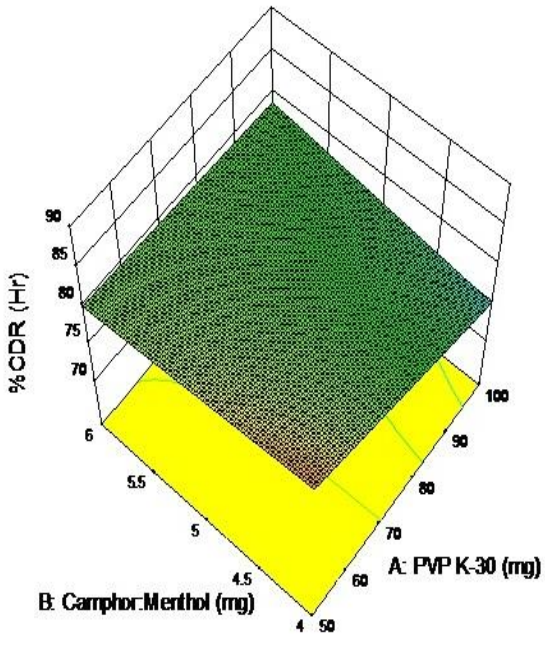
Time (Hr)	Optimized Formulation	Pure Drug Solution
1	2.03	0.04
3	7.53	1.72
6	19.58	4.06
9	36.24	11.02
12	57.27	27.23
24	79.53	36.8

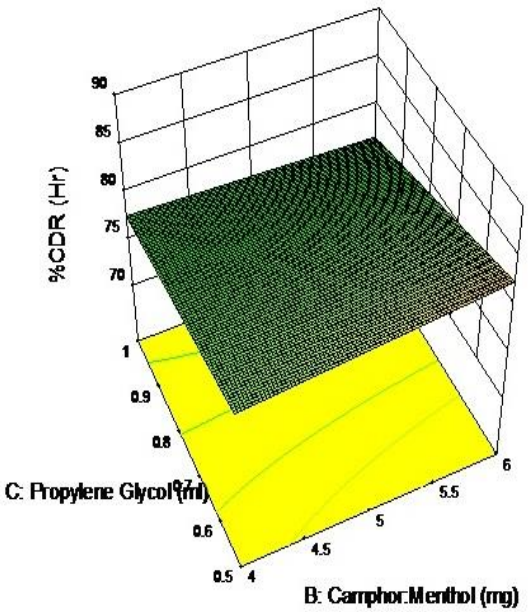
Statistical Analysis

(a) Effect of variables on % CDR

Equation:

Y_1 (% CDR) = 107.51708 - 0.45102 * X_1 (p = 0.0001) – 2.60208 * X_2 (p = 0.5676) + 3.95500 * X_3 (p = 0.0001) + 0.067550 * X_1 X_2 (p = 0.005) + 0.027000 * X_1 X_3 (p = 0.6748) - 2.97833 * X_2 X_3 (p = 0.0768)





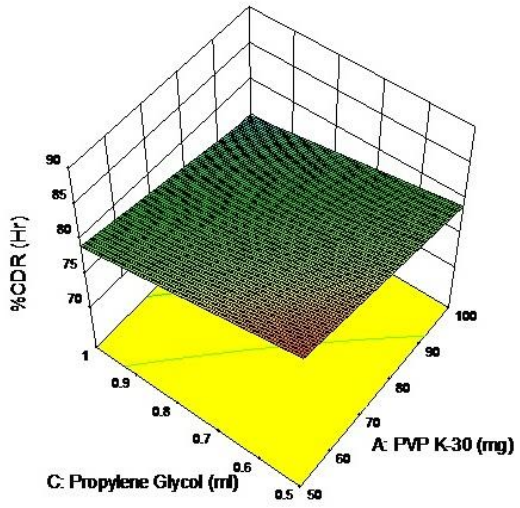


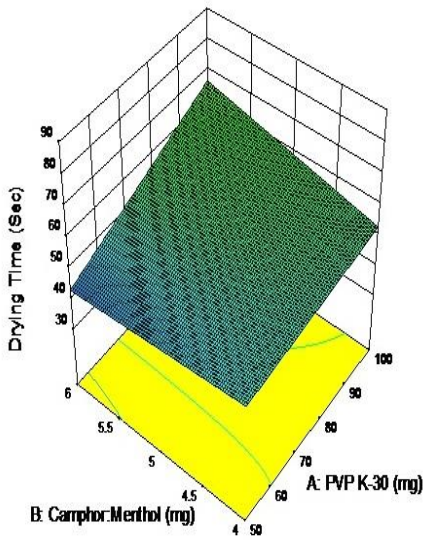
Figure No. 1: 3-D plot of %CDR

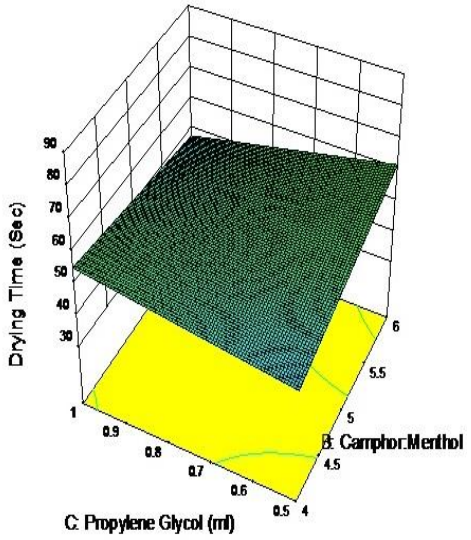
The figure shows the 3D plot, which displays when the polymer concentration decreases and permeation enhancer concentration increases it shows highest %CDR at 24 Hr. If the polymer concentration and plasticizer concentration decreases it shows highest %CDR at 24 Hr.

(b) Effect of variables on Drying Time

Equation:

Y_2 (Drying Time)= -36.34250 - 0.034433 * X_1 (p= 0.0095) + 4.53917 * X_2 (p= 0.4277) + 177.0900 * X_3 (p= 0.5748) + 0.19550 * X_1 X_2 (p= 0.0513) – 0.89387 * X_1 X_3 (p= 0.0242) - 23.07667 * X_2 X_3 (p=0.0283)





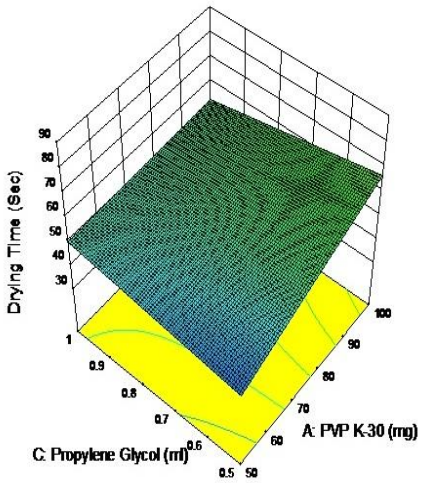


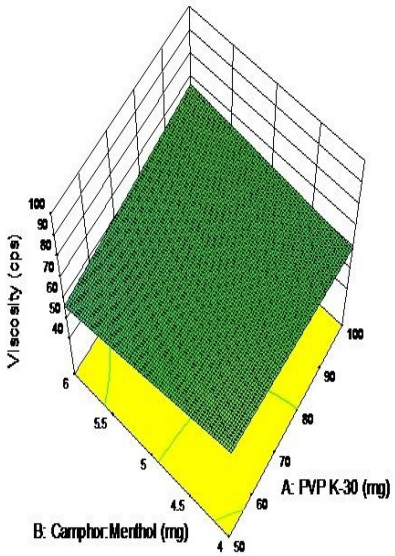
Figure No. 2: 3-D plot of Drying Time

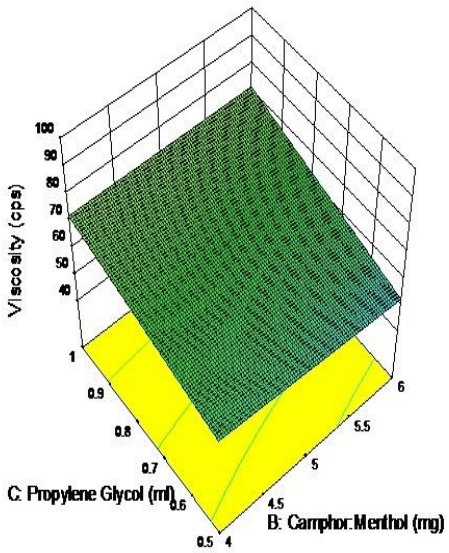
The figure shows the 3D plot, which displays the polymer and plasticizer concentration decrease it shows better drying time. If the polymer concentration increases drying time also increases.

(c) Effect of variables on Viscosity

Equation:

Y_3 (Viscosity) = 71.66375 - 0.011783 * X_1 (p = 0.09711) - 22.34875 * X_2 (p = 0.0165) + 108.78167 * X_3 (p = 0.0001) + 0.21472 * X_1 X_2 (p = 0.0001) - 1.41447 * X_1 X_3 (p = 0.0001) + 6.03833 * X_2 X_3 (p = 0.0318)





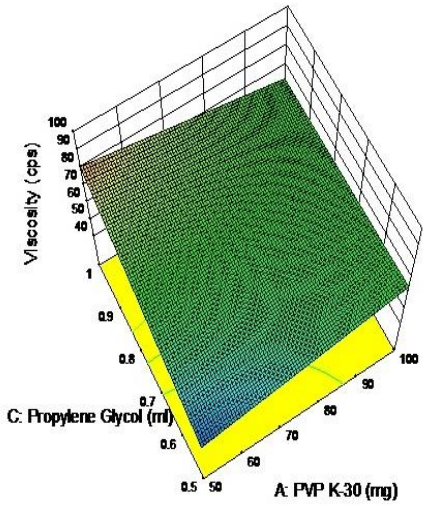


Figure No. 3: 3-D plot of Viscosity

The figure shows the 3D plot, which displays the polymer concentration decrease and plasticizer concentration increase it shows higher viscosity. If the plasticizer and polymer concentration decrease it shows better viscosity.

Fourier Transform Infrared Spectroscopy

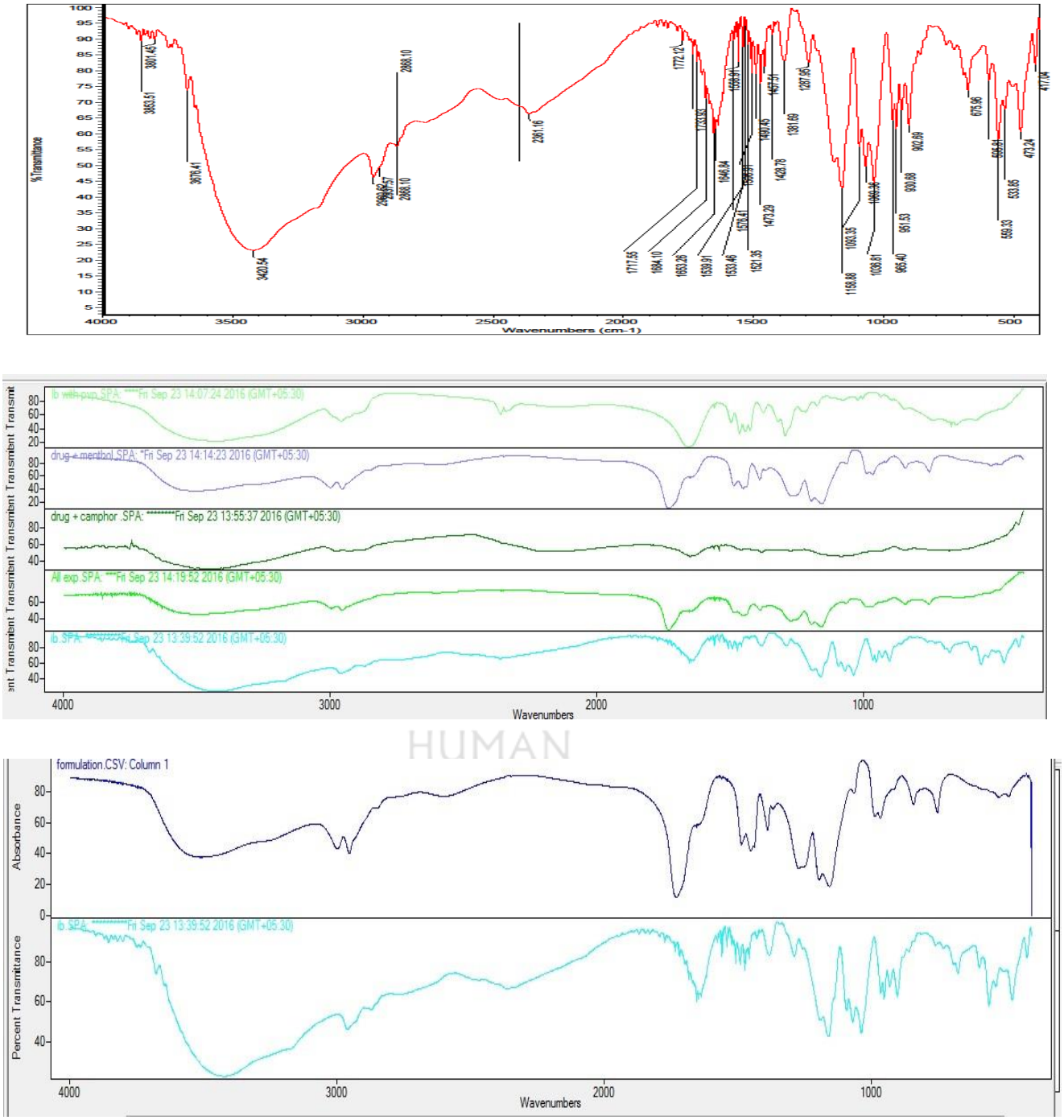


Figure No. 4: FTIR spectra of (i) API (ii) physical mixture (iii) final batch

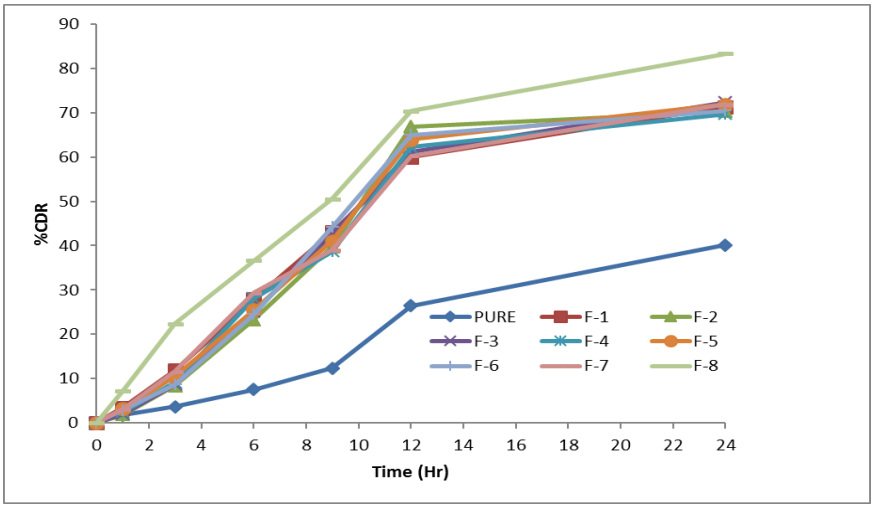


Figure No. 5: *In-vitro* drug release

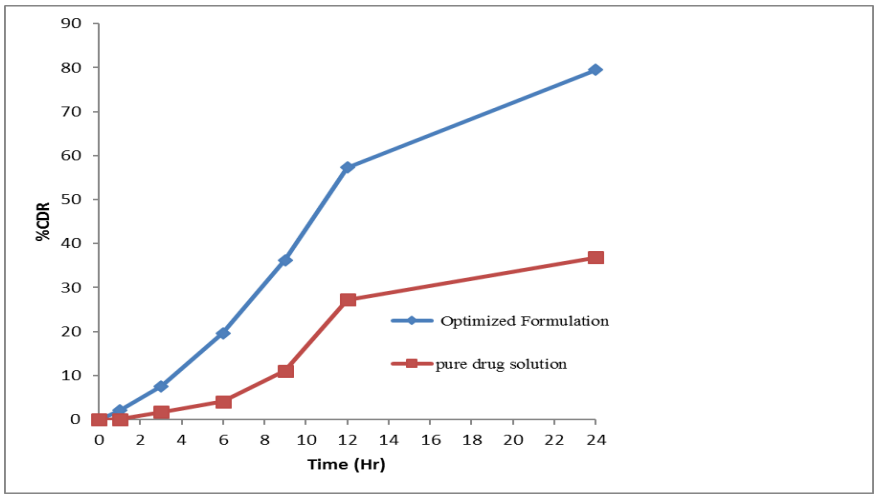


Figure No. 6: *Ex-vivo* skin permeation release

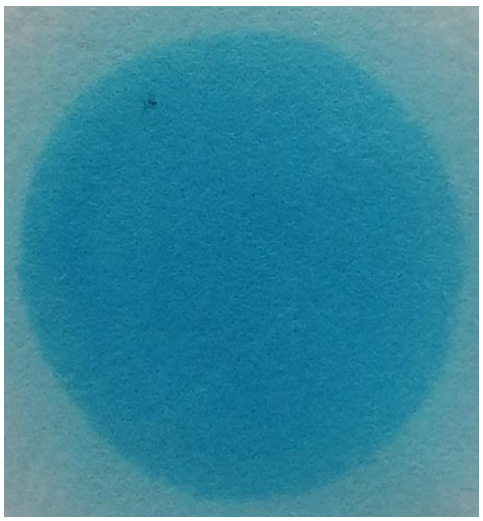
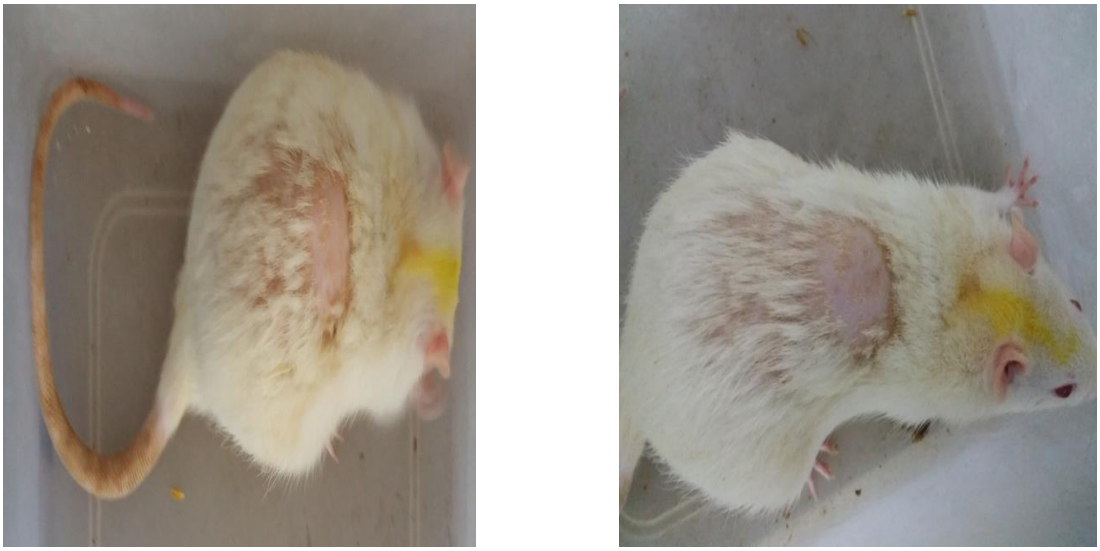


Figure No. 7: Spray Pattern



(a) After 1 Hr (b) After 24 Hr

Figure No. 8: Skin irritation

CONCLUSION

Ibandronate Sodium is an anti-osteoporotic agent used for the treatment of osteoporosis. It is a BCS Class III drug and side effects likes, GI Complication, Oesophagus Irritation and Painful or Burning Urination. Hence, drug permeation through the skin in the form of transdermal spray is a novel approach in the drug delivery system. The transdermal route selected to overcome the side effects due to the conventional oral dosage forms. Thus, it can be concluded that improved patient compliance and drug permeation has been enhanced through the transdermal route.

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