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Research Article

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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF CEFIXIME TRIHYDRATE LOADED CHITOSAN – ALGINATE TRANSDERMAL PATCHES

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ABSTRACT

Cefixime trihydrate is a third generation cephalosporin with a broad spectrum bactericidal activity. Due to its short biological half-life, it is required for frequent dosing. So, transdermal delivery system was chosen to deliver the drug directly to the systemic circulation thereby to reduce the dose as well as the frequency of dosing. Transdermal matrix patches of Cefixime trihydrate were prepared by Solvent casting method using Chitosan and Sodium alginate as polymers. Two types of Chitosan with mol.wt.190kDa and 419kDa were used. The patches prepared were found to be having good physicochemical properties. After 24 hours of in-vitro dissolution studies, the drug release was found to be maximum (89%) from the formulation FS-1. The release patterns of the patches were controlled and were found for extended period of time. The kinetic profiles show that the drug release followed zero-order kinetics and fits with Higuchi's model. The rate of drug permeation after 24hrs through rat skin was found to be 68.27% from the formulation FS-1. The drug permeation profile suggests that it followed Fick's law of diffusion. The values of the correlation coefficient were found to be linear for the Zero order release. The permeation rate was further enhanced to 87.25% with formulation FPE, by using permeation enhancer like Span-80 (1%). The permeation co-efficient of the formulations FS-1 and FPE were 17.83mg/cm^2/day and 21.32mg/cm^2/day respectively. The enhancement ratio was found to be 1.19. The On the basis of the above studies, it could be concluded that the polymer Chitosan of low molecular weight and high molecular weight, cross linked with a co-polymer like Sodium alginate could be utilized for the transdermal drug delivery of anti-bacterial drugs like Cefixime trihydrate.

Key words: Transdermal; Cefixime trihydrate; Chitosan alginate

INTRODUCTION

The future of transdermal rate controlled drug delivery is expected to grow phenomenally, and biomedical application of TDDS is expected to increase with the successful development of new approaches capable of enhancing the skin permeability of drugs. (Langer et al 2004)

Cefixime trihydrate, a broad spectrum bactericidal drug is the second largely used cephalosporin derivative in the treatment of respiratory, urinary and biliary tract infections. Controlled drug delivery systems of Cefixime trihydrate will minimize the risk associated with the unit dosage devices and definitely improve patient compliance by reducing the gastric side effects.

MATERIALS AND METHODS

Materials and their suppliers:

Cefixime trihydrate was obtained from Time Pharmaceuticals, Pondicherry. Chitosan gift samples were given by Central Institute of fisheries Technology Ltd., Cochin and Sodium Alginate was got from Molychem Labs, Mumbai. Materials like Lactic acid, Potassium dihydrogen phosphate, Sodium hydroxide and Glycerin were of laboratory grade.

Methods:

Fabrication of Transdermal patch

Solution of sodium alginate in distilled water containing Cefixime trihydrate in dissolved form was added drop wise to Chitosan solution in 2 % lactic acid under constant stirring by a magnetic stirrer. The formed coacervates were separated, poured in Petri dish and dried at room temperature to form films.

Two grades of Chitosan (molecular weights 190 Daltons and 419 Daltons) were used for the preparations. The concentration of the drug was kept constant and the concentration of the polymers Chitosan and Sodium alginate were altered as specified in the Table – 1.

Table: 1 Fabrication of matrix Transdermal patches of 3.14 Sq cm

SL. No	Formulation code	Drug (%)	Chitosan 190 kDa (%)	Chitosan 419 kDa (%)	Sodium alginate (%)	Span - 80
1	FS-1	1	1	_	1	_
2	FS-2	1	2	_	2	_
3	FS-3	1	3	_	3	_
4	FS-4	1	4	_	4	_
5	FS-5	1	2	_	4	_
6	FS-6	1	4	_	2	_
7	FIS-1	1	_	1	1	_
8	FIS-2	1	_	2	2	_
9	FIS-3	1	_	3	3	_
10	FIS-4	1	_	4	4	_
11	FIS-5	1	_	2	4	_
12	FIS-6	1	_	4	2	_
13	FPE	1	1	_	1	1

Physicochemical evaluation

Weight of the patch:

The prepared patches were weighed using a digital weighing balance and the mean value was noted.

Thickness of the Patch:

Thickness of the patch was measured by using a digital micrometer screw gauge at three different places and the mean value was calculated. (Anil J Shinde et al 2008)

Folding endurance:

The folding endurance is expressed as the number of folds the patch is folded at the same place, either to break the specimen or to develop visible cracks. This test is important to check the ability of the sample patches to withstand folding. This also gives an indication of the brittleness. The folding endurance was measured manually for the prepared film .A strip of film was cut evenly and folded at the same place till it broke .The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.(Swamy et al 2008)

Percentage of moisture absorption:

To check the physical stability of the film in high humidity condition, accurately weighed film were placed in a desiccators containing saturated solution of aluminum chloride (79.5% relative humidity) for 3 days .The film were reweighed and percentage moisture absorption were calculated using the formula. (Sankar et al 2003)

$$\text{Percentage moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Percentage of moisture loss:

To check the extent of moisture loss from freshly prepared film. Accurately weighed film were placed in a desiccator containing fused anhydrous calcium chloride for 72 hrs .After 72 hrs the film were reweighed and percentage moisture loss was calculated using the formula . (kusum Devi et al 2003)

$$\text{Percentage moisture lost} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity:

The prepared patch was cut into small piece and put into 100ml dissolution or diffusion medium used respectively and Stirred continuously in an electrical shaker and sample was withdrawn at the end of three hours and the drug content was determined, spectrophotometrically at 288nm. (GS Sanap et al 2008)

Mechanical strength (Tensile strength and Elongation strength):

The patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance travelled by the pointer before break of the patch was calculated as kg/cm^2. (Saraf Swarnalate et al 2006)

Water Vapour transmission rate:

The patches were fixed over the edge of the glass vial containing 3g of fused calcium chloride as a desiccant by using an adhesive. Then the vial was placed in a desiccator containing saturated solution of potassium chloride. The vial was taken out periodically and weighed for a period of 72 hours. (Kulkarni Raghavendra et al 2000)

In- vitro release study:

The drug release study was performed using USP XXIII dissolution test apparatus, modified paddle over disk method was used at 50 rpm rotation and 900 ml of phosphate buffer pH 7.2 at 32^0C .Transdermal patch of 3.14cm^2 was placed in a modified disk assembly i.e. sandwiched between the glass and the mesh. Samples were withdrawn at predetermined intervals, filtered and analyzed spectrophotometrically at 288nm using corresponding medium as blank. After each withdrawal the same quantity of fresh medium was replaced immediately.

Stability study:

The patches were stored for three months at temperature 40^0C± 2^0C and at a relative humidity of 75%. The stability study was conducted with regard to tensile strength, moisture content and drug content. The patches, which retained their physical properties, were further subjected to in-vitro permeation studies.

In-vitro skin permeation studies:

The experiments were performed in accordance with the guidelines for animal use specified by the CPCSEA. The approval was given by the Institutional Animal Ethical Committee formed for this purpose. (Protocol No:SVCP/IAEC/M.Pharm/02/2008-09 dt. 24.12.08.)

These studies were carried out using rat abdomen skin of required thickness. The permeation cell used for this study was a specially fabricated "Franz diffusion cell". A 2.5 cm diameter patch was placed in intimate contact with the stratum corneal side of the skin; the topside was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 60 ml of Phosphate buffer pH 7.2 solution. The whole assembly was kept on a magnetic stirrer, at a speed of 50 rpm and the temperature conditions controlled at 32^0C $\pm$ 0.5^0 C. The cell contents were stirred with a magnetic stirrer. Sample of 1 ml was withdrawn at pre-determined time intervals and simultaneously replaced with equal volume of fresh medium. The samples were withdrawn and filtered through Whattman filter paper. The absorbance of the solution was measured by UV at 288 nm. (GS Sanap et al 2008)

Permeation enhancement ratio:

The Permeation enhancement ratio was calculated from the kinetic study of both the formulations with and without permeation enhancer (FS-1 and FPE). It was calculated from the following parameters. (R Sadashivaiah et al 2008)

Permeability coefficient (P):

Permeability coefficient is the velocity of drug passage through the membrane in µg/cm ^{2} /h. The permeability coefficient was calculated from the slope of the graph of percentage of drug transported versus time as,

P = Slope x Vd / S

Where, Vd is the volume of donor solution and S is the surface area

Flux (J):

Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time. It is calculated by,

Flux (J) = P x CD

where CD = concentration of donor solution and P = permeability.

Enhancement ratio:

Enhancement ratio was used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules. It is calculated by,

$$\text{Enhancement Ratio (\%)} = \frac{\text{Permeability coefficient of drug with enhancer}}{\text{Permeability coefficient of drug alone}}$$

Skin irritation test:

The rabbits were divided into 5 groups with three each. On the previous day of the experiment, the hair on the back side of the rabbit was removed.

Group – I: served as normal, without any treatment

Group – II: Control- applied with marketed official adhesive tape in USP

Group – III: Blank – applied with drugless polymeric patches.

Group – IV: Test – applied with drug loaded polymeric patches

Group – V: applied with 0.8%v/v aqueous solution of formalin solution as Standard irritant

The animals were applied with new patch / formalin solution each day up to 7days and finally the application sites were graded according to a visual scoring scale. (Srinivas Mutalik et al 2005)

The erythema scale is as follows:

0 - none

1 - Slight

2 - Well defined

3 - Moderate

4 - Scar formation

The edema scale is as follows:

0 - none

1 - Slight

2 - Well defined

3 - Moderate

4 – Severe

Ethical clearance for the handling of experimental animals was obtained from the Institutional animal ethical committee (IAEC) formed for this purpose.

Results

The Drug, polymers and the fabricated transdermal patches with combination of Chitosan and Sodium alginate were subjected to various evaluation parameters like compatibility studies using FTIR absorption spectra , thickness of the patch, folding endurance, Percentage of moisture absorption , Percentage of moisture loss, Preparation of calibration curve, Drug content uniformity, in-vitro dissolution studies ,in-vitro skin permeation studies and Skin irritation test.

Table – 2

Code	*Thickness (mm)	*Weight (mg)	*Folding endurance	*Tensile strength gm/mm²	*Elongation at break (%)	*% Moisture absorbed	*% Moisture Lost	WVT Rate mg/cm²/h	Drug content (%)
FS-1	0.192 ±0.001	7.51 ±0.15	373± 2	0.225 ± 0.002	30.20 ± 0.100	6.073 ±0.004	0.280 ±0.001	0.132 ± 0.006	98.25 ± 0.05
FS-2	0.264 ±0.001	9.20 ±0.26	386± 2	0.232 ± 0.003	29.83 ± 0.115	6.214 ±0.003	0.168 ±0.001	0.166 ± 0.001	97.96 ± 0.15
FS-3	0.385 ±0.002	10.25 ±0.03	416± 3	0.314 ± 0.001	37.60 ± 0.173	6.826 ±0.002	0.423 ±0.001	0.281 ± 0.026	98.41 ± 0.20
FS-4	0.411 ±0.001	11.72 ±0.02	401± 4	0.426 ± 0.011	24.51 ± 0.076	7.162 ±0.003	0.795 ±0.002	0.256 ± 0.003	98.01 ± 0.45
FS-5	0.421 ±0.002	12.42 ±0.02	367± 2	0.341 ± 0.001	22.40 ± 0.100	7.420 ±0.001	0.896 ±0.001	0.343 ± 0.012	98.26 ± 0.20
FS-6	0.311 ±0.001	11.15 ±0.02	392± 2	0.324 ± 0.002	20.93 ± 0.057	7.243 ±0.015	0.812 ±0.001	0.252 ± 0.012	98.21 ± 0.27
FIS-1	0.212 ±0.002	8.12 ±0.02	362± 3	0.232 ± 0.001	29.40 ± 0.100	6.120 ±0.020	0.274 ±0.001	0.075 ± 0.005	98.31 ± 0.12
FIS-2	0.286 ±0.002	9.72 ±0.01	374±2	0.240 ± 0.003	27.30 ± 0.100	6.240 ±0.020	0.162 ±0.001	0.138 ± 0.007	98.51 ± 0.07
FIS-3	0.394 ±0.004	11.06 ±0.49	400± 1	0.313 ± 0.001	36.50 ± 0.100	6.666 ±0.015	0.436 ±0.001	0.263 ± 0.009	98.35 ± 0.05
FIS-4	0.420 ±0.017	12.06 ±0.20	394± 1	0.446± 0.001	22.80 ± 0.100	7.12 ±0.025	0.802 ±0.001	0.271 ± 0.017	98.25 ± 0.05
FIS-5	0.431 ±0.010	12.81 ±0.01	356± 2	0.362 ± 0.002	20.10 ± 0.115	7.50 ±0.100	0.874 ±0.001	0.249 ± 0.018	98.06 ± 0.37
FIS-6	0.361 ±0.001	11.67 ±0.01	380± 2	0.327 ± 0.001	21.50 ± 0.100	7.27 ±0.249	0.841 ±0.001	0.241 ± 0.022	98.05 ± 0.49

*Average of three values ± Standard deviations

The weights ranged between 7.51 mg and 12.81 mg observed for all prepared Transdermal films. The folding endurance and tensile strength lied in between 356 and 416 and 0.225 gm/sq.mm and 0.446gm/sq.mm and the difference depend on the composition of polymer used. The drug dissolution and diffusion profiles show that as the concentration of the polymer is increased, the rate of drug release/permeation is also decreased.

In vitro dissolution profile of various formulations

Table: 3

Time (hrs)	Cumulative % Drug release					
	FS-1	FS-2	FS-3	FS-4	FS-5	FS-6
0	0	0	0	0	0	0
0.25	4.411	4.453	2.663	1.024	1.957	1.185
0.5	9.573	7.250	5.765	4.260	2.448	3.121
0.75	13.18	10.75	8.283	7.607	4.647	5.353
1	16.37	13.70	11.29	9.826	6.055	7.284
2	20.63	16.78	13.00	11.99	8.301	9.390
3	23.02	19.49	16.17	14.75	11.59	13.01
4	26.34	22.43	18.43	17.34	14.04	15.09
5	30.51	25.48	20.65	19.96	17.05	18.49
6	34.19	27.79	22.56	23.11	19.98	21.81
7	38.21	30.42	25.43	26.48	24.07	25.74
8	42.04	34.22	26.20	29.31	27.35	28.37
9	47.10	36.31	27.41	32.90	29.45	31.11
10	50.75	41.53	32.36	35.47	34.32	36.72
12	56.24	46.88	43.49	41.12	39.79	42.64
16	67.21	60.80	52.70	52.92	51.25	50.40
20	78.52	74.10	66.07	63.98	64.90	65.24
24	89.47	86.52	79.51	74.29	77.38	76.62

In vitro dissolution plot of various formulations

Comparative drug release plot

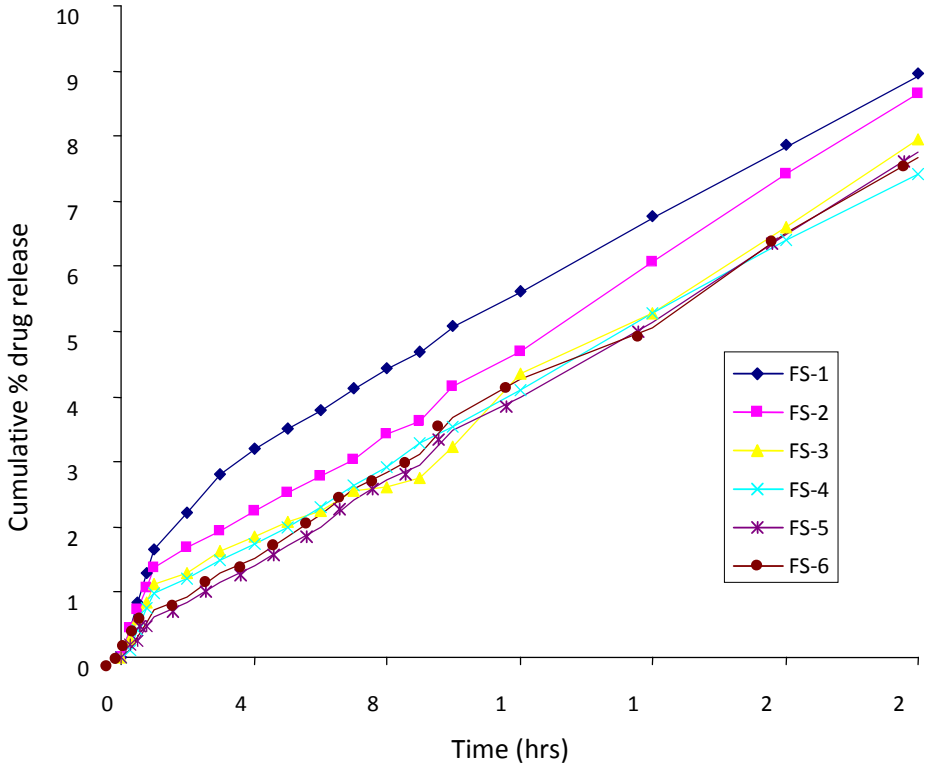


Figure: 1 In vitro dissolution profiles of various formulations

Table: 4

Time (hrs)	Cumulative % drug release					
	FIS-1	FIS-2	FIS-3	FIS-4	FIS-5	FIS-6
0	0	0	0	0	0	0
0.25	3.342	2.322	1.555	1.427	1.385	0.745
0.5	5.808	3.646	3.645	2.153	3.048	1.045
0.75	8.438	5.014	4.970	3.626	4.266	2.133
1	10.91	6.810	6.084	4.248	5.060	3.073
2	13.67	9.225	12.03	6.235	9.242	7.231
3	15.84	12.66	15.65	8.394	11.14	9.136
4	18.25	15.43	18.54	9.097	14.19	12.09
5	20.44	18.60	21.44	11.35	17.00	15.61
6	23.38	20.02	22.14	13.51	19.05	17.27
7	26.38	23.43	25.22	16.21	22.06	20.70
8	28.48	26.38	27.31	19.15	24.45	22.11
9	30.99	29.60	30.39	22.18	28.46	27.08
10	33.11	33.58	32.36	25.33	30.47	28.68
12	40.32	41.46	37.85	31.03	34.13	32.38
16	55.48	54.14	42.73	42.55	46.31	44.77
20	69.38	67.03	57.10	53.47	53.78	56.91
24	82.21	78.18	72.85	64.01	70.46	68.05

In vitro dissolution plot of various formulations

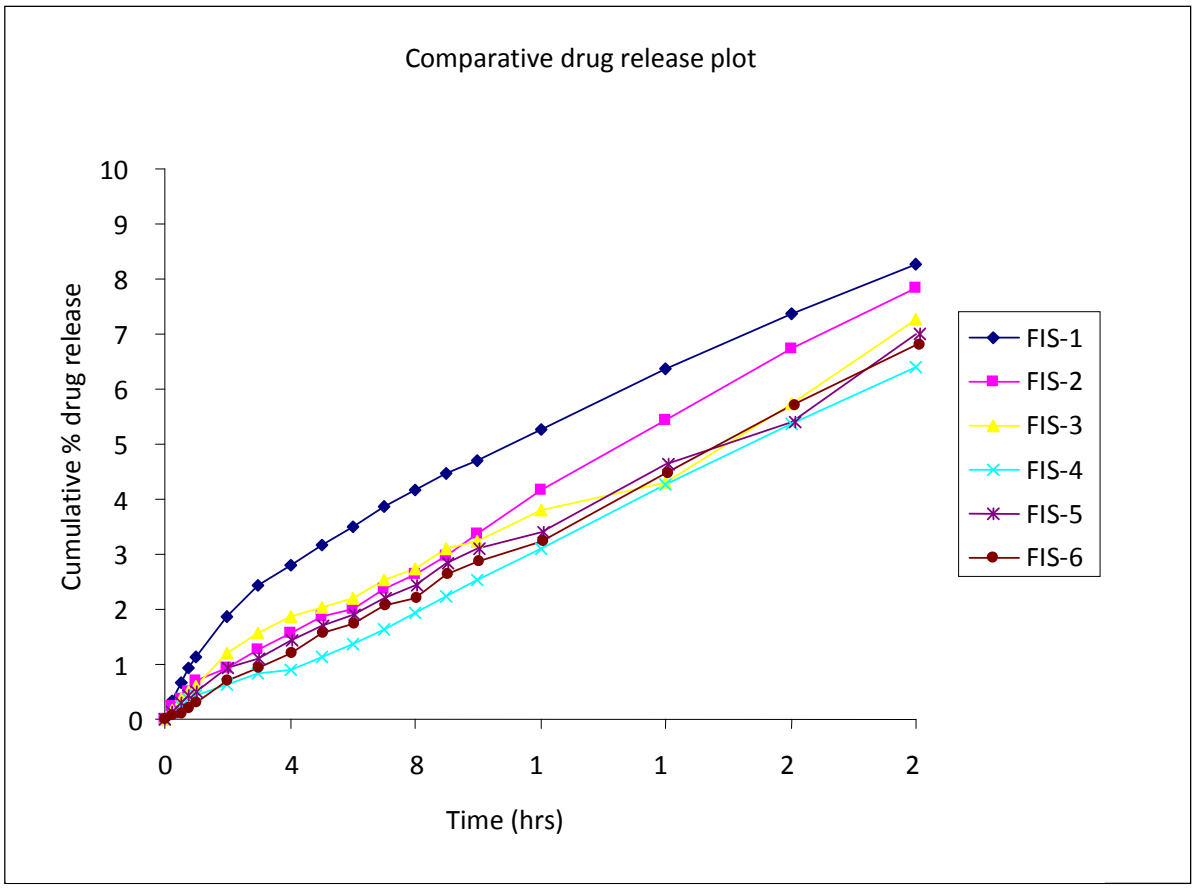


Figure: 2

Kinetic Profile of In-vitro drug release from various formulations

Table: 5

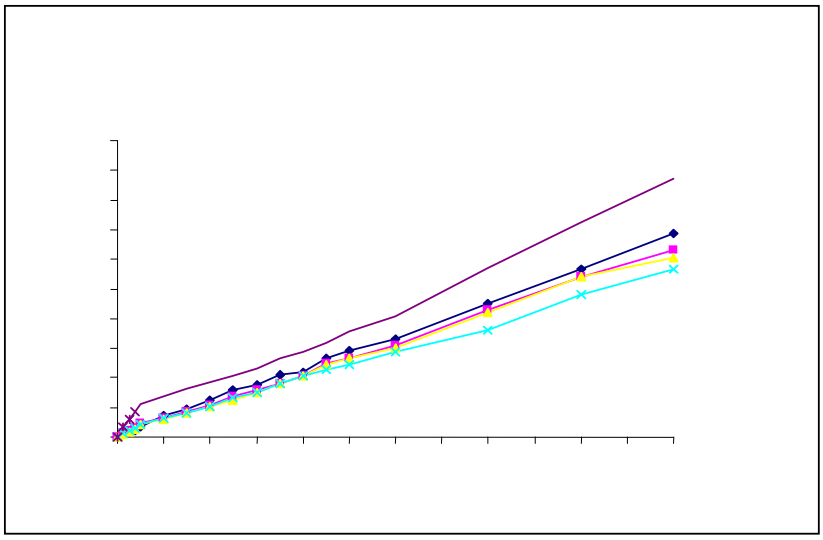
Formulation Code	Zero-order			First-order		Higuchi		Korse Meyer Peppa's		Possible mechanism of drug release
	n	R^2	Release rate constant	n	R^2	n	R^2	n	R^2	
FS-1	3.4789	0.9526	3.4789	0.0351	0.9505	18.168	0.9918	0.5277	0.9923	zero-order, Non-fickian
FS-2	3.3586	0.9897	3.3586	0.0304	0.9362	17.128	0.9473	0.6022	0.9516	zero-order, Non-fickian
FS-3	3.0687	0.9871	3.0687	0.0243	0.9358	15.551	0.9173	0.635	0.9266	zero-order, Non-fickian
FS-4	3.0056	0.9919	3.0056	0.0223	0.9781	15.522	0.9592	0.6775	0.9691	zero-order, Non-fickian
FS-5	3.166	0.9988	3.166	0.0239	0.9583	16.297	0.9396	0.8407	0.9858	zero-order, Non-fickian
FS-6	3.1378	0.9954	3.1378	0.0236	0.9669	16.23	0.9525	0.7839	0.9823	zero-order, Non-fickian
FIS-1	3.1859	0.9913	3.1859	0.0264	0.9259	16.132	0.9183	0.652	0.9405	zero-order, Non-fickian
FIS-2	3.2134	0.9977	3.2134	0.0249	0.9559	16.46	0.9318	0.7954	0.9776	zero-order, Non-fickian
FIS-3	2.7647	0.9821	2.7647	0.0196	0.9503	14.313	0.9547	0.7121	0.9866	zero-order, Non-fickian
FIS-4	2.6268	0.9948	2.6268	0.0171	0.9635	13.368	0.9043	0.8996	0.9712	zero-order, Non-fickian
FIS-5	2.7557	0.9951	2.7557	0.0189	0.9637	14.217	0.9465	0.8063	0.9938	zero-order, Non-fickian
FIS-6	2.8091	0.9987	2.8091	0.0189	0.9708	14.528	0.9416	0.9443	0.9969	zero-order, Non-fickian

In-vitro skin permeation of selected formulations

Table: 6

Time	Cumulative % of Drug Permeation				
	FS-1	FS-2	FIS-1	FIS-2	FPE
0	0	0	0	0	0
0.25	1.022	1.470	0.958	1.214	3.504
0.5	1.791	1.983	1.663	2.111	5.880
0.75	2.304	2.944	2.496	3.008	8.528
1	3.266	4.546	4.097	4.098	11.23
2	7.233	6.277	5.827	6.346	13.88
3	9.478	8.713	8.071	8.073	16.16
4	12.29	10.63	10.11	10.11	18.37
5	15.83	13.78	12.37	13.27	20.62
6	17.38	15.97	15.20	15.20	23.34
7	20.85	18.10	18.03	18.03	26.60
8	22.09	20.74	20.67	20.67	28.63
9	26.59	24.79	24.27	22.87	31.62
10	28.98	26.41	26.41	24.62	35.81
12	32.85	30.73	30.14	28.55	40.59
16	44.91	42.72	42.13	36.12	56.92
20	56.65	54.27	53.88	47.92	72.62
24	68.74	62.90	60.33	56.73	87.25

In vitro permeation profiles of various formulations



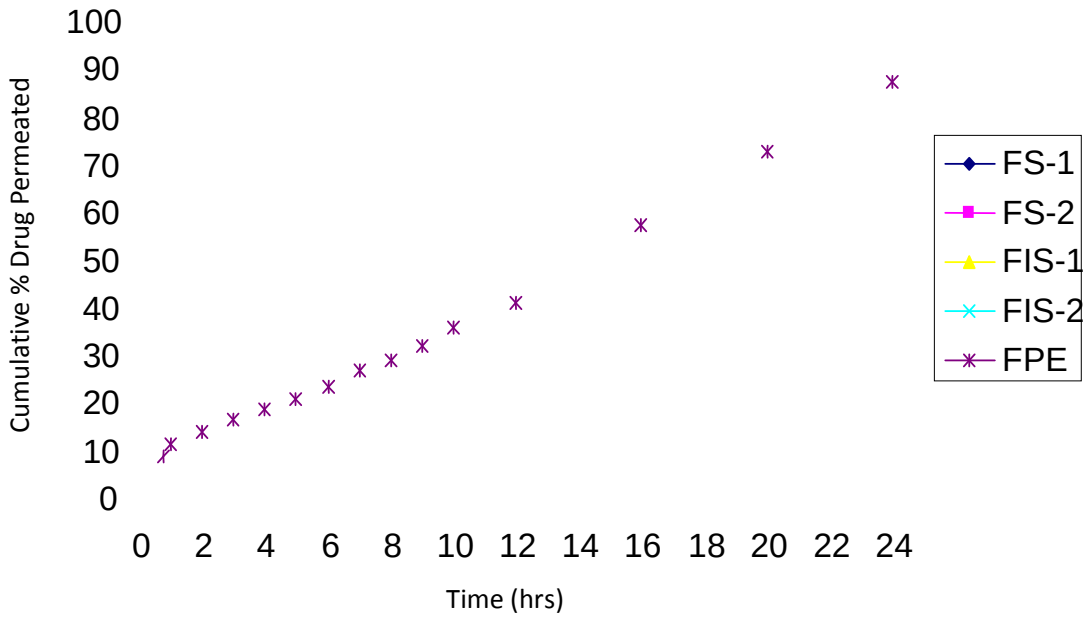


Figure: 3

PERMEATION ENHANCEMENT RATIO

The Permeation enhancement ratio was calculated from the comparison of the permeation coefficients of the two formulations. It is shown in the tabular column.

Table: 7

Formulation Code	Slope	Permeation coefficient (mg/cm²/day)	Flux	Enhancement Ratio
FS-1 (without enhancer)	2.8002	17.83	3.56	1.196
FPE (with enhancer)	3.3488	21.33	4.26	

SKIN IRRITATION TEST:

The visual score was 0 (none) on the edema scale and 1 (slight) on the erythema scale. This indicates there was no sign of skin reaction. This shows the suitability of the prepared patches for transdermal use.

DISCUSSION

In the present study, transdermal matrix patches of Cefixime trihydrate were prepared by Solvent casting method using Chitosan and Sodium alginate as polymers. The patches were found to be having good film formation and smooth in their appearance. The flexibility was also very good and fulfilled the physico-chemical evaluations. The compatibility studies were done by FT-IR Spectroscopy. The FT-IR spectral analysis showed that there were no physical and chemical interactions between the drug and polymers and they were found to be compatible with each other. The drug content Percentage yield was in the range 97.96% to 98.51%.

A good tensile strength was found in all the films, ranging from 0.225± 0.002 to 0.446± 0.0017 g/cm $^{2.}$ The moisture content in the preparations was found to be low. This helps the formulations to be stable and prevents them from drying and brittle. Moisture uptake ranged from 6.073 to 7.5%.Low moisture uptake protects the materials from microbial contamination and avoids bulkiness of the patches. The percentage moisture loss ranged between 0.162 to 0.896% which prevents the films from drying. During dissolution, the sodium alginate present in the film absorbs a significant amount of water to hydrate, swell and form a stable hydrogel. The drug embedded in the Chitosan alginate film is immobilized in the polymer matrix because of the cross linked gelation.

The change in the polymer concentration had a change on the release rate of the drug. As the concentration increases, the drug release is decreased. After 24 hours, the drug release was found to be the maximum from formulation FS-1 and lowest percentage of drug release was seen from formulation FIS-4.The kinetic profile show that the drug release followed zero-order kinetics and well fits with Higuchi's model. The diffusion followed non-fickian release.

There is an increase in drug release with the increase in the concentration of Sodium alginate two fold of the concentration of Chitosan. Formulations FS-5, FS-6, FIS-5 and FIS-6 with altered concentrations of Chitosan and Sodium alginate show better results than the formulations with equal proportions of the polymers. This might be due to the cross linking and internal gelling capacity of Sodium alginate. All the formulations followed zero-order kinetics and non-fickian diffusion pattern. The formulations also fit well with Higuchi's kinetic model. The release patterns of the patches were controlled and spread over extended period of time. The values of the coefficient of correlation (r) were calculated and were found to be linear for the Zero order release. The In-vitro drug release data were fitted to Korse Meyer Peppa's release model. The 'n' values were in the range of 0.6 to 0.9. This indicates that the drug release mechanism was diffusion and non-fickian transport. These formulations also showed higher 'r' values for zero-order kinetics rather than first – order kinetic indicating that the release is by diffusion mechanism.

The formulations with Chitosan, molecular weight-190 kDa showed the drug release in the range of 74% to 89% in 24 hrs study. The formulations with Chitosan, molecular weight – 419kDa showed drug release in the range of 68.05% to 82.21% in the In-vitro dissolution study for a period of 24hrs. Initially, rapid release was observed, thereby confirming the controlled release behavior of the formulations. The initial quick release would

be beneficial as it would help achieve a therapeutic plasma concentration of the drug in minimum time and the constant release obtained later would then provide a sustained and controlled release of the drug. The burst effect might be due to initial migration of the drug towards the surface of the matrix.

The results show that the release of the drug is based on the concentration of the polymers rather than the molecular weight of Chitosan. Both the types of Chitosan show almost closer percentage of drug release. The formulation FS-1, with lowest concentrations of both the polymers appears to be the best choice for developing a matrix transdermal delivery system for Cefixime trihydrate.

The formulations that showed better drug release during the In-vitro dissolution were chosen for the further stability analysis. The In- vitro stability studies of the patches were performed in terms of stability against storage conditions and aging effect. The physical characterization like tensile strength, moisture absorption and WVT rate and drug content were main parameters for stability studies, which showed no appreciable changes occurred in patches.

The formulations which were stable in their physical nature and showed more the 80% of drug release (FS-1; FS-2; FIS-1 and FIS-2) were selected and they were subjected to In-vitro skin permeation studies. The drug permeation profile suggests that it followed Fick's law of diffusion. Linear relationship between cumulative percent drug permeated verses time indicate zero order permeation of drug through rat abdomen skin.

The permeation profile of drug from the patches FS-1, FS-2, FIS-1, and FIS-2 between permeation data against square root of time shows linear relationship indicating drug permeation followed Higuchi equation. The permeation profile data of patches were plotted in log values with time, the slope value comes near (~ 0.5), suggesting drug permeation is controlled by diffusion. Among the permeation of various formulations, FS-1 system provides maximum permeation i.e., 68.27% of drug. The results show that formulation FS-1 had all satisfactory Physico-chemical characteristics and it shows the maximum release rate of the drug during the In-vitro dissolution and In-vitro skin permeation studies. To enhance the permeation of the drug, the best formulation was once again modified with a permeation enhancer like Span-80 (1%) and it was studied for its In-vitro skin permeation profile. A permeation rate of 87.25% was achieved with the use of Span-80(1%) and study showed that with the permeation enhancer, the rate of permeation was increased considerably. So, further improvement of the drug permeation can be brought by modification of the polymer concentration as well as that of the permeation enhancer.

The permeation co-efficient of the formulations FS-1 (without permeation enhancer) and FPE (with permeation enhancer) were 17.83 mg/cm^2 / day and 21.32 mg/cm^2 / day respectively which indicate that the use of permeation enhancer like Span-80(1%) improves the permeation of the drug considerably. The enhancement ratio was also found to be in the appreciable range (1.19).

Skin irritation studies were performed as per the standard method. It showed that there was no edema seen and only a very slight erythema was found during the test. This shows that the prepared patches can be utilized for transdermal use.

CONCLUSION

On the basis of the *in vitro* skin permeation study, it could be concluded that the polymer Chitosan of low molecular weight and high molecular weight, cross linked with a co-polymer like Sodium alginate could be utilized for the transdermal drug delivery of anti-bacterial drugs like Cefixime trihydrate. The formulations yielded desired drug release by zero-order kinetics. Linear regression analysis of the drug dissolution profile and the drug diffusion profile showed that the mechanism of drug release was following diffusion pattern. The transdermal patches we made could provide the delivery of drug at a controlled rate across intact skin and might be used in clinical situations. The formulations definitely improve patient compliance and reduce the gastric side effects. However, these results cannot be directly extrapolated to humans, as rodent skin is generally more permeable than human skin. Further work is to be carried out for establishing the therapeutic utility of these systems by carrying out detailed pharmacokinetic and pharmacodynamic studies in humans.

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