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FORMULATION AND *INVITRO* EVALUATION OF TRANSDERMAL GEL CONTAINING KETOPROFEN SILVER NANOPARTICLES

P. Sowjanya[1], P. Aparna [2], Ch.Srilatha[3], M. Ravi Kumar[4]

[1]Department of Pharmaceutics, Geethanjali College of Pharmacy, Cheryaal, Secunderabad, Telangana.

[2,3]Assistant Professor, Geethanjali College of Pharmacy, Cheryaal, Secunderabad, Telangana.

[4]Principal, Geethanjali College of Pharmacy, Cheryaal, Secunderabad, Telangana.

Abstarct:

Ketoprofen, (RS)-2-(3-benzoylphenyl)-propionic acid (chemical formula $C_{16}H_{14}O_3$) is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin. In the present research work transdermal gel containing ketoprofen silver nanoparticles were prepared and characterized eight formulations were prepared by using different concentrations of carbopol 931 and 974 various evaluation tests were performed like spreadability, viscosity, drug content, pH determination and drug release . Using diffusion cell the drug release was determined among all the formulations FG6 shown maximum drugb release of 97.47% in 12 hours. Optimized formulation followed zero order release kinetics.

Key words: *Ketoprofen, carbopol 931 and 974*

Corresponding Author:

P. Sowjanya,

Department of Pharmaceutics,
Geethanjali College of Pharmacy,
Cheryaal, Secunderabad, Telangana.
puttasowji3@gmail.com

QR code

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INTRODUCTION:

Nanoparticles are small particles which are made up of non-biodegradable and biodegradable polymers. Their diameter is from 1-1000 nm. These systems were developed in early 1970s. This approach was attractive because the methods of preparation of particles were simple and easy to scale-up. The particles formed were stable and easily freeze dried.

Among drugs used in the treatment of arthritis, ketoprofen (Keto) (phenyl propionic acid) which belongs to a group of drugs called nonsteroidal anti-inflammatory drugs has been widely used. It acts by inhibiting the production of prostaglandin with analgesic and antipyretic effects. However, the disadvantages of Keto are short half-life time, about 1.5–2 h after using oral dosage form, and irritation caused in the gastrointestinal mucous membrane In order to avoid the side effects and enhance the usage of drugs, drug nanoparticles have been developed and investigated since the 1970s. Nanoparticles with submicron size (10–1000 nm) have more advantages than conventional dosage formulations. They include improved efficacy, reduced toxicity, increased ability and controlled drug delivery.

MATERIALS AND METHODS:

Ketoprofe, Carbopol 934, Carbopol 971, PEG 4000, Methanol, Diethyl ether chemicals were Laboratory grade made of SD Fine chemicals Pvt Ltd

Preparation of Standard Calibration Curve of Ketoprofen:

100 mg of Ketoprofen was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with pH 6.8 phosphate buffer to prepare stock solution. The 10 ml of stock solution was further diluted with pH 6.8 phosphate buffer in 100ml to get 100µg/ml (working standard). Then 2,4,6,8 and 10 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with pH 6.8 phosphate buffer. Then the absorbance was measured in a UV spectrophotometer at 258 nm against pH 6.8 phosphate buffer as blank.

Method of Preparation of Ketoprofen Loaded Silver Nanoparticles:

Synthesis of Ag nanoparticles using tri sodium citrate (TSC) as a reducing agent.

Silver nitrate and tri sodium citrate were used as starting materials for the preparation of silver nanoparticles. The silver colloid was prepared by using chemical reduction method. All solutions of reacting materials were prepared in distilled water. In typical experiment 50 ml of 0.001 M, 0.01 M, 0.1 M $AgNO_3$ was heated to boil. To this solution 5 mL of 1 % trisodium citrate was added drop by drop. During the process, solutions were mixed vigorously and heated until change of colour was evident (pale yellow). Then it was removed from the heating device and stirred until cooled to room temperature.

Table 1: Composition of the Silver nanoparticles

Formulations	$AgNO_3$	Trisodium Citrate	Water	Drug
F1	0.001 M	1 %	50 ml	100mg
F2	0.01 M	1 %	50 ml	100mg
F3	0.1 M	1 %	50 ml	100mg

The mechanism of reaction could be expressed as follows **(Silva, E. I.et al, 2007, Hangxun, 2010)**

$$4Ag+ + C_6H_5O_7Na_3 + 2H_2O \rightarrow 4Ago + C_6H_5O_7H_3 + 3Na^+ + H^+ + O_2\uparrow$$

The colloidal solution of silver nanoparticles was characterized by using UV-Visible spectroscopy and SEM.

Characterization:

Scanning Electron Microscopy (SEM): Scanning Electron Microscopy (SEM) was used to record the photo micrographic images of synthesized AgNP's. A small volume of AgNP's suspension was taken for SEM analysis.

Table 2: Composition of different emulgel formulations

Formulation (F)	Carbopol 934 (mg)	Carbopol 971 (mg)	Poly ethylene glycol4000(mg)	Methanol (ml)	Diethyl ether (ml)	Water
F_1	75		10	15	0.05	Q.s
F_2	100		10	15	0.05	Q.s
F_3	125		10	15	0.05	Q.s
F_4	150		10	15	0.05	Q.s
F_5		75	10	15	0.05	Q.s
F_6		100	10	15	0.05	Q.s
F7		125	10	15	0.05	Q.s
F8		150	10	15	0.05	Q.s

Evaluation Of Ketoprofen Loaded Silver Nanoparticles:

1. Particle size
2. Zeta potential
3. SEM
4. FTIR

Formulation of Nanoparticulate Hydrogel

Preparation of Nanoparticle loaded carbopol gels Gel forming polymer (Carbopol) was soaked in water for 24 hours and then dispersed by agitation to get a smooth dispersion. The dispersion was allowed to stand for 15 min to expel entrapped air. Simultaneously nanoparticles, propylene glycol, permeation enhancer was added to water and undergoes gentle stirring. This was added to carbopol mixture by stirring, triethanolamine is added to form gel.

Evaluation of prepared gel

Spreadability, viscosity, drug content, pH determination and drug release are the various evaluation tests performed for the prepared gels.

RESULTS & DISCUSSION:

Standard Calibration curve of Ketoprofen:

Table 3: Concentration and absorbance obtained for calibration curve of Ketoprofen In pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 258 nm)
1	2	0.107
2	4	0.215
3	6	0.299
4	8	0.402
5	10	0.507

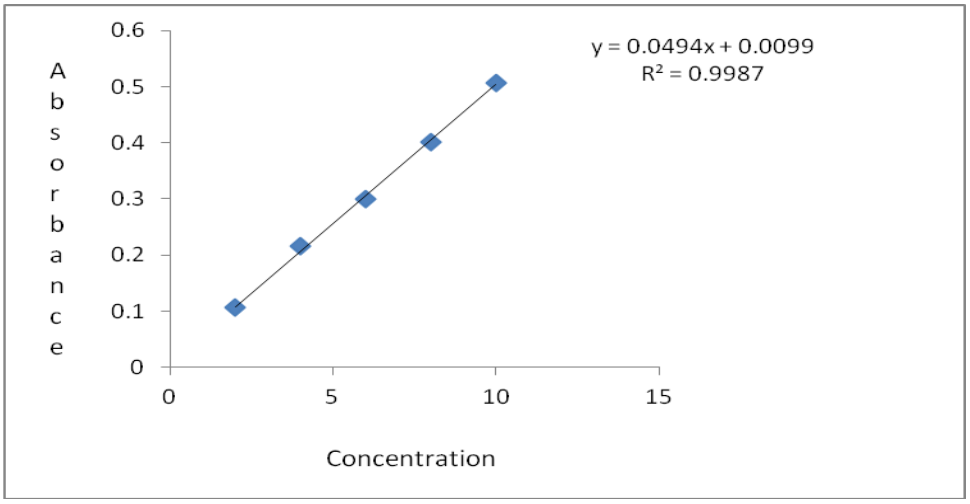

Fig 1: Standard graph of Ketoprofen in pH 6.8 Phosphate buffer

Among three formulations the formulation prepared with a concentration of 0.1M $AgNO_3$ was produced a clear product hence it is considered as optimized formulation.

Table 4: Evaluation of the prepared silver nanoparticles loaded transdermal gel

Formulation code	Drug content	pH	Spreadability(cm/sec)	Viscosity(poise)
FG1	97.23	6.9	4.2	8,775
FG2	98.55	6.7	3.9	8,943
FG3	98.16	6.3	3.6	8,861
FG4	99.34	6.7	2.9	10,741
FG5	98.16	6.4	3.5	10,492
FG6	98.55	6.5	3.7	9,812
FG7	98.16	6.8	3.3	12,098
FG8	99.25	6.8	3.6	10,576

***In-Vitro* Drug Release Studies**

Table 5: In-Vitro drug release data

TIME (h)	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8
0	0	0	0	0	0	0	0	0
0.5	2.34	2.68	2.89	2.59	12.5	12.87	18.81	19.89
1	7.04	6.18	9.09	7.65	15.34	16.77	29.02	28.04
2	8.01	8.59	17.98	15.27	20.54	22.09	35.7	35.43
3	20.31	12	28.87	18.73	45.78	33.03	43.32	41.65
4	28.15	23.96	38.77	26.3	57.55	47.15	49.25	47.18
5	32.17	31.27	46.78	32.57	61.6	55.38	55.28	53.81
6	41.07	40.79	57.77	40.03	67.63	60.19	60.92	58.89
7	49.03	49.33	68.98	55.62	70.2	73.38	66.08	64.53
8	56.5	56.92	75.43	61.35	75.76	80.27	70.44	69.43
9	69.15	69.06	81.34	72.53	79.86	85.44	81.9	73.44
10	73.39	78.12	85.67	79.87	81.6	87.24	85.27	76.89
11	77.87	82.34	88.93	82.34	83.82	91.56	89.56	79.98
12	81.78	85.67	92.67	89.03	86.88	97.47	92.33	83.98

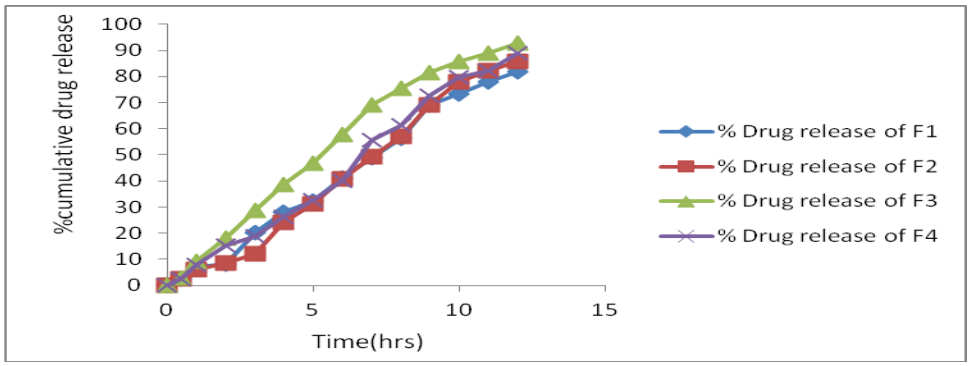

Fig 2: % drug release of the formulation F1-F4

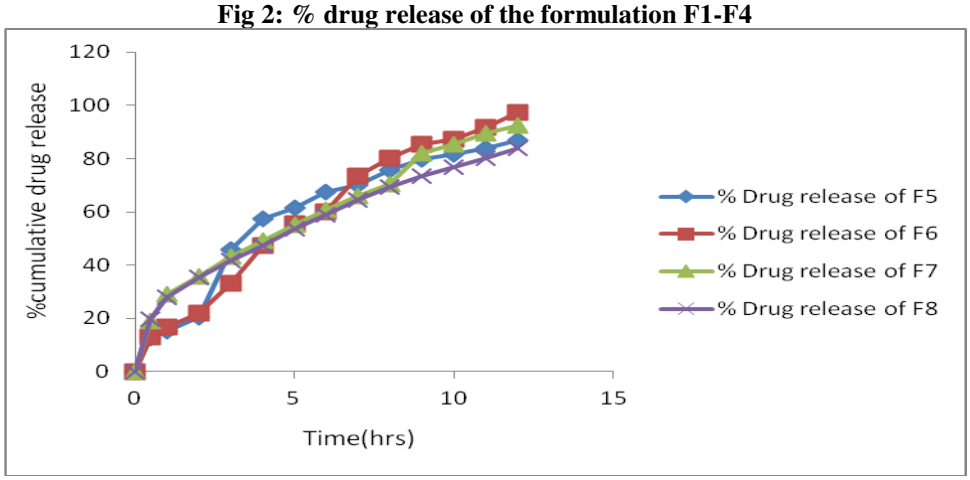

Fig :3 % drug release of the formulation F5-F8

Table 6:Kinetics Data Of F6

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
12.87	0.5	0.707	1.110	-0.301	1.940
16.77	1	1.000	1.225	0.000	1.920
22.09	2	1.414	1.344	0.301	1.892
33.03	3	1.732	1.519	0.477	1.826
47.15	4	2.000	1.673	0.602	1.723
55.38	5	2.236	1.743	0.699	1.650
60.19	6	2.449	1.780	0.778	1.600
73.38	7	2.646	1.866	0.845	1.425
80.27	8	2.828	1.905	0.903	1.295
85.44	9	3.000	1.932	0.954	1.163
87.24	10	3.162	1.941	1.000	1.106
91.56	11	3.317	1.962	1.041	0.926
97.47	12	3.464	1.989	1.079	0.403

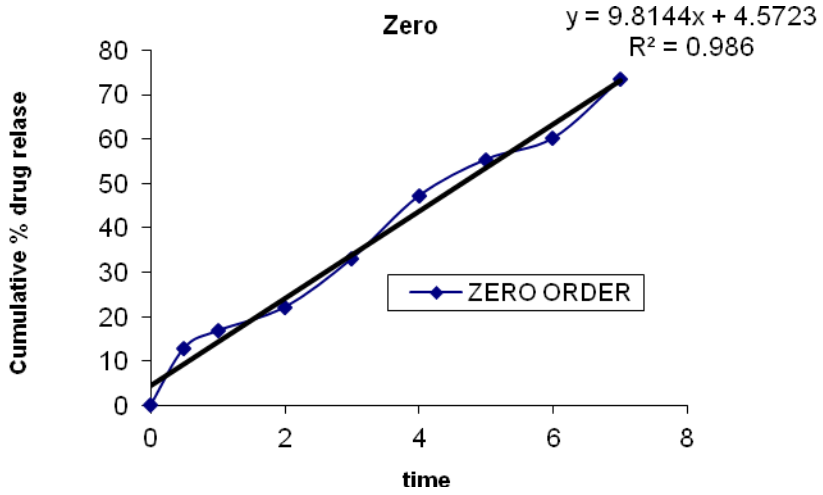

Fig 4: zero order- kinetic model

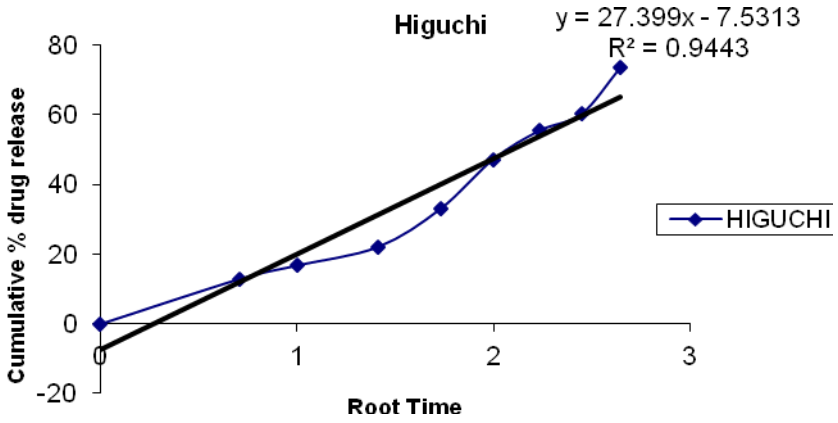

Fig 5 : higuchi model-kinetic model

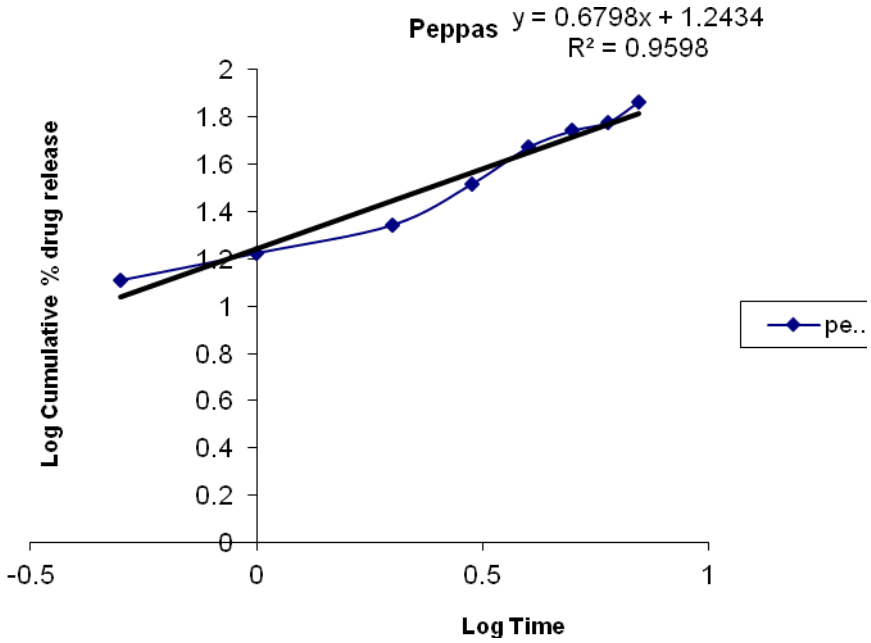

Fig 6: Peppas- kinetic model

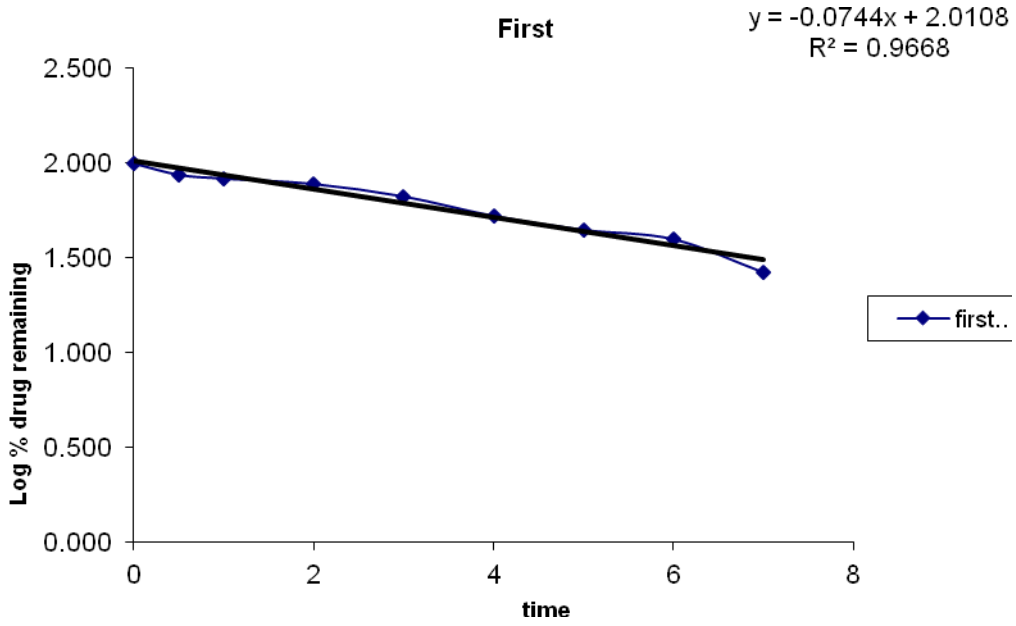

Fig 7:First order- kinetic model

CONCLUSION:

Transdermal route offers several potential advantages over conventional routes. These advantages includes avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in the blood levels, and most important it provides patient convenience. In the present research work transdermal gel containing ketoprofen silver nanoparticles were prepared and characterized eight formulations were prepared by using different concentrations of carbopol 931 and 974 various evaluation tests were performed like

spreadability, viscosity, drug content, pH determination and drug release . Using diffusion cell the drug release was determined among all the formulations FG6 shown maximum drugb release of 97.47% in 12 hours. Optimized formulation followed zero order release kinetics.

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