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FORMULATION AND EVALUATION OF ETHENZAMIDE EMULGEL

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ABSTRACT

Emulgel is one of the recent technologies in the Novel drug delivery system used for dual control release of emulsion and gel for topical use. The method used for the preparation of microemulsion w/o was the water titration method with Liquid paraffin and propylene glycol as oil phase, Tween 80 and Span 80 are used as surfactants and its concentration were fixed based on pseudo ternary phase diagrams. The optimized emulsion formulation was incorporated into the gel matrix that is Carbopol-934, HPMC-5, and HPMC-15 + Carbopol-934 by using various concentrations. The prepared Emulgel was characterized for drug content, physical appearance, pH, viscosity, spreadability, extrudability, and *in vitro* drug release studies. The optimized formulations showed F9 with 1:3 HPMC-15 + Carbopol-934 formulations showed *in vitro* drug release of 97.82% at the end of 5 hours. The optimized formulation showed good drug release within the specified limits. Ethenzamide was proven to be a suitable candidate for formulating Emulgel for topical delivery to achieve better patient compliance.

KEYWORDS: Ethenzamide, Emulgel, Topical application, Carbopol-934, HPMC-5, HPMC-15 + Carbopol-934, Liquid paraffin, Tween 80, Span 80, and Propylene glycol.

INTRODUCTION

Drugs are delivered topically for their action at the site of application or to show the systemic effect. The absorption of the drug through the skin is improved if the drug substance is in solution, if it has a favorable lipid/water partition coefficient and if it is a non-electrolyte. For their local action, the drug applied to the skin comprises antiseptics, antifungal agents, skin emollients & protectants. The main advantage of a topical delivery system is to bypass first-

pass metabolism. Molecules can enter the skin by three routes: through intact stratum corneum, through sweat ducts, or through sebaceous follicles.

EMULGEL is a combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion are used as a vehicle to deliver various drugs to the skin. They also have high ability to penetrate the skin. The presence of a gelling agent in the water phase converts a classical emulsion into an Emulgel. Emulgel for dermatological use has several favorable properties such as being thyrotrophic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent and pleasing appearance.

MATERIALS AND METHODS

Drug is provided by SURA LABS and other chemicals like Triethanolamine, Liquid paraffin, Span 80, Tween 80, Propylene glycol, Methylparaben, Carbopol-934, HPMC-5, Alcohol are provided by Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development

a) Determination of absorption maxima: 100 mg of Ethenzamide pure drug was dissolved in 15 ml of Methanol and makeup to 100 ml with 0.1N HCL (stock solution-1). 10 ml of the above solution was taken and makeup with 100 ml by using 0.1 N HCL (stock solution-2 i.e. 100 µg/ml). From this 10 ml was taken and makeup with 100 ml of 0.1 N HCl (10µg/ml). Scan the 10 µg/ml using a Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation of calibration curve: 100 mg of Ethenzamide pure drug was dissolved in 15 ml of Methanol and volume made up to 100 ml with 0.1N HCL (stock solution-1). 10 ml of the above solution was taken and made up with 100 ml by using 0.1 N HCl (stock solution-2 i.e. 100 µg/ml). From this take 1, 2, 3, 4, 5, and 6 ml of solution and makeup to 100 ml with 0.1N HCl to obtain 1, 2, 3, 4, 5, and 6 µg/ml of Ethenzamide solution. The absorbance of the above dilutions was measured at 230 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-axis and absorbance on Y-axis which gives a straight line. Linearity of the standard curve was assessed from the square of correlation coefficient (R2) which was determined by least squares linear regression analysis. The experiment was performed in triplicate and based on average absorbance; the equation

for the best line was generated. The results of standard curve preparation are shown in Table- and figure.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy: Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drugs and other excipients. In the current study 1:1 ratio was used for the preparation of physical mixtures used for analyzing compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using the direct sample technique.

Method of preparation

STEP 1: Preparation of emulsion using oil phase and water phase by emulsification method. Drugs can be incorporated either in the oil or the aqueous phase depending upon their solubility.

STEP2: Formulation of gel base by using hydrocolloids by soaking in warm water.

STEP3: In the third step after cooling, a prepared emulsion is incorporated into the preformed gel and stirred to uniform disperse emulsion into the gel base.

Preparation of Ethenzamide Emulgel: Different formulations were prepared using varying amounts of gelling agent. The method only differed in process of making gel in different formulations. The preparation of emulsion was the same in all the formulations. The gel bases (Carbopol 934, HPMC-5, and HPMC15+Carbopol-934) were prepared by dispersing in distilled water separately with constant stirring at a moderate speed using a mechanical shaker. Formulations F1, F2, and F3 were prepared by Carbopol 934; F4, F5, and F6 by HPMC5; F7, F8, and F9 by HPMC15 + Carbopol-934 as a gelling agent. In formulations, the gel was prepared by dispersing the base in heated distilled water (75°C) and the dispersion was cooled and left overnight. The pH of all the formulations was adjusted to 5.5 to 6.5 using tri-ethanol amine (TEA). The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methylparaben was dissolved in propylene glycol and mixed with the aqueous phase Ethenzamide being hydrophobic was dissolved in the oil phase. Both the oily and aqueous phases were separately heated to 70° to 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained

emulsion was mixed with the gel in a 1:1 ratio with gentle stirring to obtain the Emulgel. The composition of different formulations has been discussed in following table.

Characterization of Gellified Emulsion

1. Physical appearance: The prepared Emulsion formulations were inspected visually for their color, homogeneity, consistency, and pH. The pH values of 1% aqueous solutions of the prepared gellified Emulsion were measured by a pH meter (Digital pH meter).

2. Rheological Study: The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories) and connected to a thermostatically controlled circulating water bath.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	114.408	114.408	114.408	114.408	114.408	114.408	114.408	114.408	114.408
Carbopol-934	1	1.5	2.0	-	-	-	-	-	-
HPMC-5	-	-	-	1.0	1.5	2.0	-	-	-
HPMC15+Carbopol-934	-	-	-	-	-	-	1	1.5	2.0
Triethanolamine	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Liquid paraffin	4	4	4	4	4	4	4	4	4
Alcohol	2	2	2	2	2	2	2	2	2
Span 80	3	3	3	3	3	3	3	3	3
Tween 80	1	1	1	1	1	1	1	1	1
Propylene glycol	5	5	5	5	5	5	5	5	5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

3. Spreadability: Spreadability is determined by the apparatus suggested which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured based on 'Slip' and 'Drag' characteristics of Emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm.) under study is placed on this ground slide. The Emulgel is then sandwiched between this slide and another glass slide having the dimension of a fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to a pull of 80 gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula:

S= M.L/T

Where, S = spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides from each other.

4. Extrudability study: It is a usual empirical test to measure the force required to extrude the material from the tube. The method applied for the determination of applied shear in the region of the rheogram corresponds to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating Emulgel formulation for extrudability is based upon the quantity in the percentage of Emulgel and Emulgel extruded from a lacquered aluminum collapsible tube on the application of weight in grams required to extrude at least 0.5 cm ribbon of Emulgel in 10 seconds. More quantity extruded better is Extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is then calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (in gm.) / Area (in cm)

5. Drug Content Determination: Drug concentration in gellified Emulsion was measured by spectrophotometer. The drug content in gellified Emulsion was measured by dissolving a known quantity of gellified Emulsion in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in a UV/VIS spectrophotometer (UV -1700 CE, Shimadzu Corporation, Japan).

6. *In Vitro* Release Study: Franz diffusion cell (with an effective diffusion area of 3.14 cm and 15.5 ml cell volume) was used for the drug release studies. Gellified Emulsion (200 mg) was applied onto the surface of the egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time intervals. Samples were analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drugs released at each time interval. The cumulative amount of drug released across the egg membrane was determined as a function of time.

RESULTS AND DISCUSSION

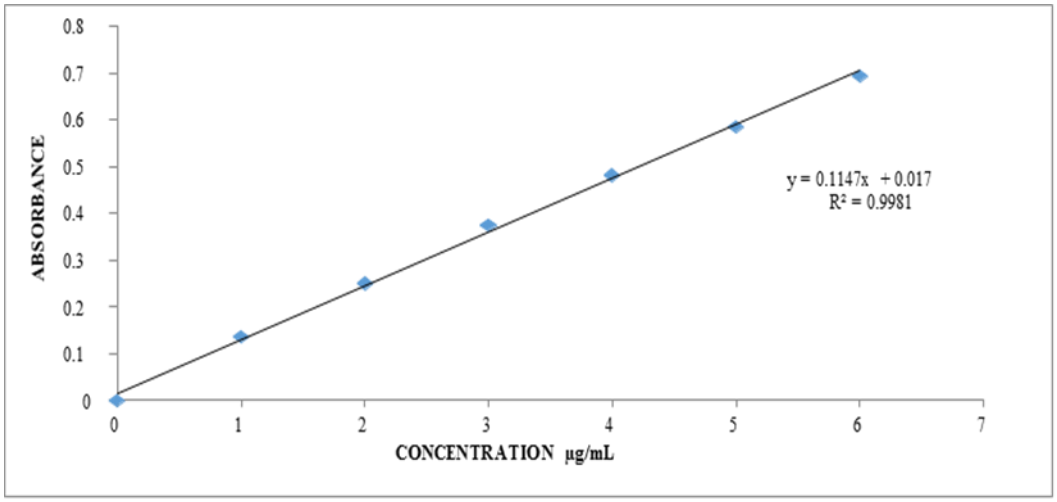
A unique feature of topical drug delivery is the direct accessibility of the skin as a target organ for diagnosis and treatment. The topical drug delivery system offers several advantages

over oral drug delivery systems. The oral drug delivery system produced many side effects so to overcome the side effect of the oral dosage form, the drug was formulated into a topical drug delivery system i.e. Emulgel. Emulgel formulation of Ethenzamide was prepared using 4 types of gelling agents: Carbopol934, HPMC-5, and HPMC15+ Carbopol-934 as polymers. Ethenzamide is used for topical as well as Anti-inflammatory diseases. In the present study, an attempt was made to formulate topical Emulgel of the drug for efficient delivery of the drug across the skin.

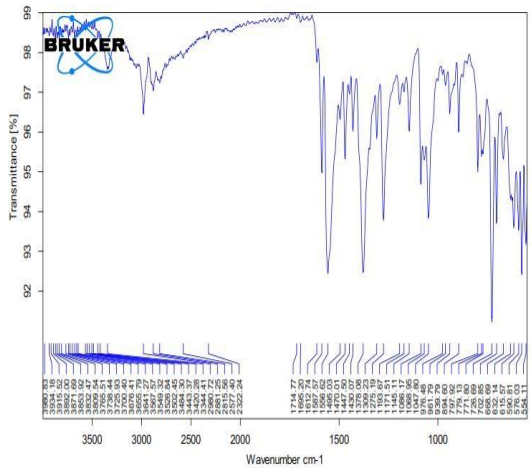
Analytical Method

Standard graph of Ethenzamide in 0.1N HCl: The scanning of the 10 µg/ml solution of Ethenzamide in the ultraviolet range (200- 400 nm) against 0.1 N HCl, the maximum peak was observed at λ_{max} as 230 nm. The standard concentrations of Ethenzamide (1-6 µg/ml) was prepared in 0.1N HCl showed good linearity with r^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law.

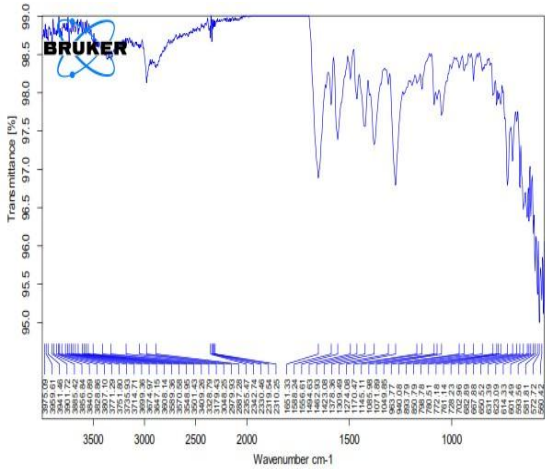
Concentration (µg/ml)	Absorbance
1	0.128
2	0.254
3	0.371
4	0.482
5	0.597
6	0.824



FTIR study



FTIR graph of pure drug



FTIR graph of optimized formulation

From the FTIR data, it was evident that the drug and excipients do not have any interactions. Hence, they were compatible.

Physical Examination: The prepared gellified emulsion formulations were white, viscous, and creamy preparations, with a smooth and homogeneous appearance, as given in the table. The incorporation of propylene glycol as a humectant not only provided the optimum spreadability to the product but also improved the aesthetic appearance. HPMC15 + Carbopol-934 as a gelling agent helped to achieve the desired viscosity, thereby affecting the homogeneity as well as the spreadability of the final preparations. There was no sign of phase separation in any of the preparations. The results are given in the following table.

Table: Physicochemical characteristics of Emulgel.

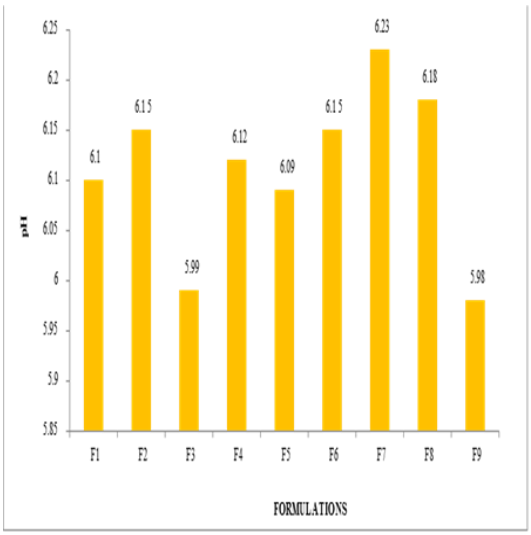
S.No.	Formulation code	Colour	Phase separation	Grittiness	Homogeneity	Consistency
1	F1	White	None	-	Fair	+
2	F2	White	None	-	Fair	+
3	F3	White	None	-	Fair	+
4	F4	White	None	-	Good	++
5	F5	White	None	-	Good	++
6	F6	White	None	-	Good	++
7	F7	White	None	-	Excellent	+++
8	F8	White	None	-	Excellent	+++
9	F9	White	None	-	Excellent	+++

Measurement of pH

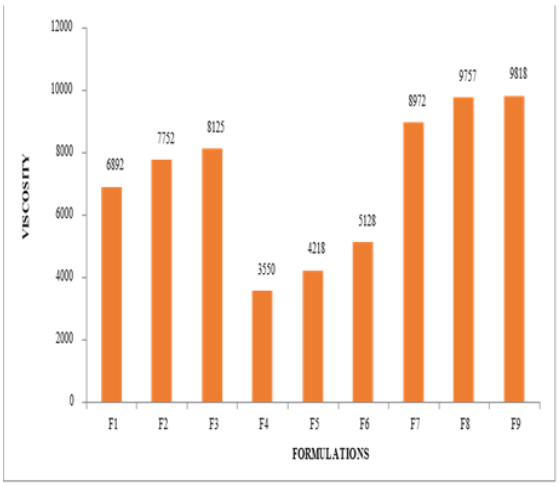
The pH of Emulgel formulations was determined by using a digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and it was placed for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated. The pH of the Emulgel formulations was in a range that lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The data is reported in the table.

Table No. 8.4: Different formulations Parameters.

S. No.	Formulation code	pH	Viscosity	Spreading Coefficient	Extrudability	Drug content
1	F1	6.10	6892	16.6	10.8	98.19
2	F2	6.15	7752	18.3	11.3	99.51
3	F3	5.99	8125	16.9	13.6	98.36
4	F4	6.12	3550	21.6	9.1	97.85
5	F5	6.09	4218	28.1	10.5	98.11
6	F6	6.15	5128	32.3	11.4	99.14
7	F7	6.23	8972	33.3	12.3	99.35
8	F8	6.18	9757	35.4	15.6	98.16
9	F9	5.98	9818	39.8	17.6	100.05



pH of F1-F9 formulations



viscosity of F1 – F9 formulations

Viscosity

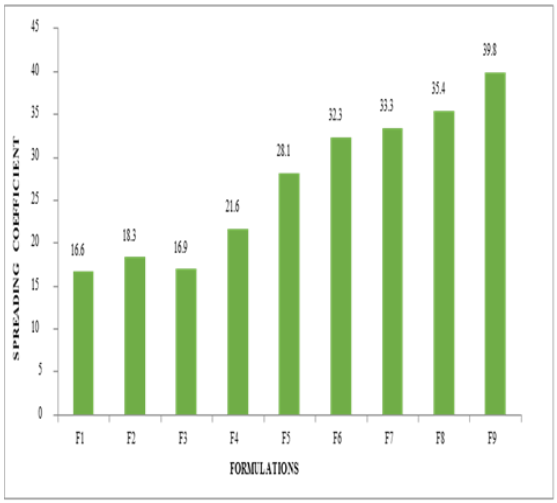
All of the prepared formulations possessed optimum viscosity. Since the type and quantity of the gelling agent in each formulation were the same, the inclusion of different bases has brought about some difference in the viscosity of the gellified emulsions. While F9 was the most viscous formulation, F4 had the least viscosity.

Spreadability

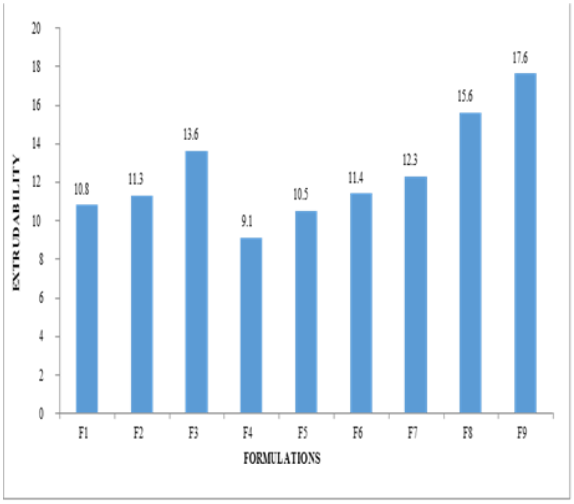
The values of the spreadability indicated that the gellified emulsions were easily spreadable by a small amount of shear. Formulation F9 gave the highest value for spreadability.

Extrudability

The gels were filled into collapsible tubes after formulating them. The extrudability of the formulation has been checked and the results were shown in figure.



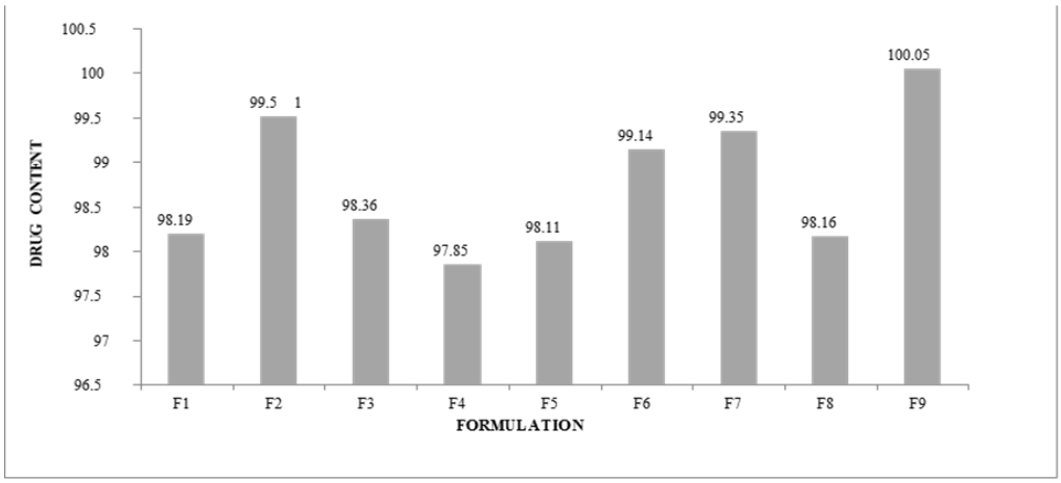
Spreadibility of F1 – F9 formulations



Extrudability of F1 – F9 formulations

Drug content

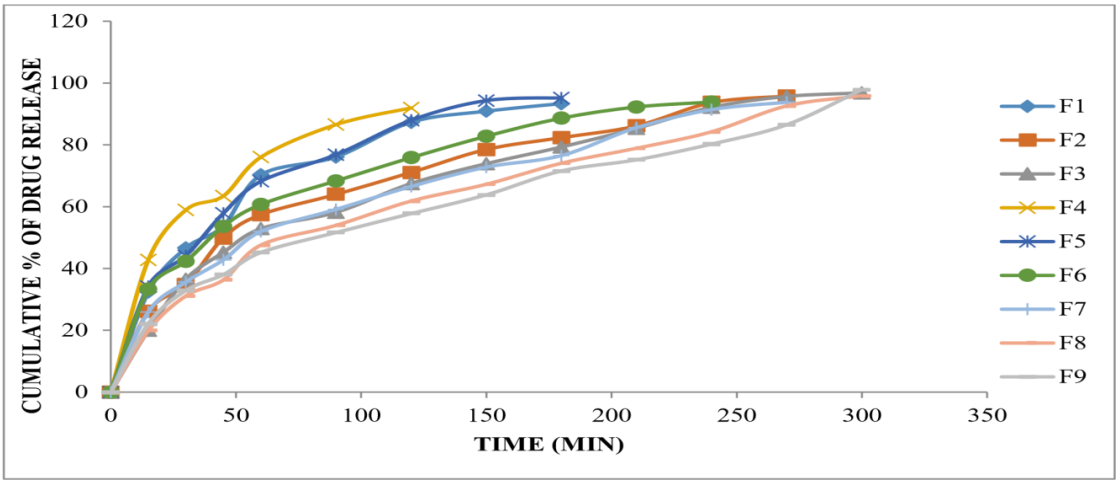
The percent drug content in gellified emulsions was found to fall in the range of 97.85 to 100.05.



Drug content of F1-F9 formulations

Diffusion study of Emulgel containing Ethenzamide by using various polymers

TIME (MIN)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	32.39	26.13	20.03	42.80	34.19	33.31	25.94	19.96	22.14
30	46.62	34.81	36.53	58.93	44.11	42.29	35.63	31.13	32.91
45	53.78	49.94	45.24	63.46	57.89	53.64	42.80	36.31	38.01
60	70.31	57.43	52.90	76.04	68.23	60.72	51.99	47.60	45.20
90	76.10	63.97	58.18	86.57	76.85	68.34	59.12	53.96	51.63
120	87.32	71.08	67.49	91.94	87.98	75.87	66.54	61.83	57.76
150	90.89	78.50	73.91		94.33	82.79	72.79	67.24	63.81
180	93.35	82.32	79.30		95.19	88.64	76.52	74.06	71.56
210		86.13	85.37			92.26	85.58	78.90	75.16
240		93.69	92.16			93.83	91.40	84.23	80.26
270		95.74	95.66				93.76	92.61	86.51
300			96.81					95.90	97.82



Diffusion study of Emulgel containing Ethenzamide with Carbopol-934, HPMC-5 and HPMC15+ Carbopol-934 (F1 to F9)

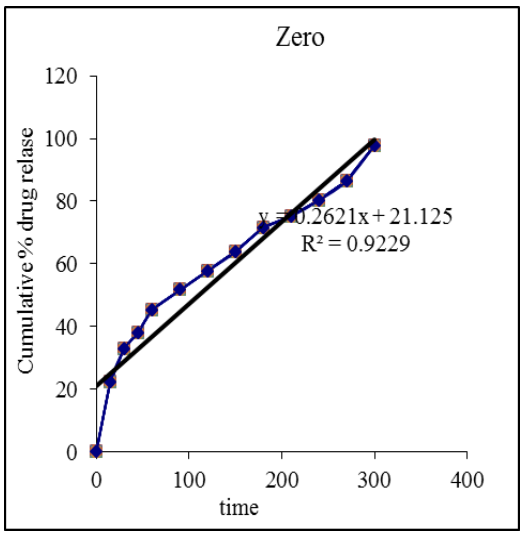
Pharmacokinetics

Application of Release Rate Kinetics to drug diffusion Data

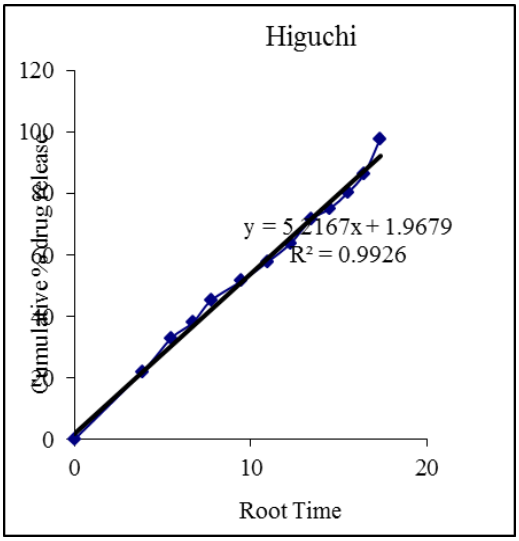
Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Ethenzamide release from Sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Release kinetics data for optimized formulation (F9)

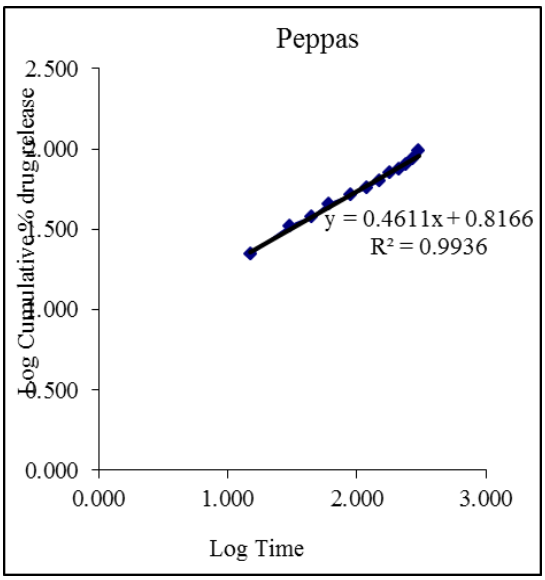
Time (T)	Cumulative (%) Release	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	RELEASE RATE (CUMULATIVE % RELEASE / t)
0	0	0			2.000	
15	22.14	3.873	1.345	1.176	1.891	1.476
30	32.91	5.477	1.517	1.477	1.827	1.097
45	38.01	6.708	1.580	1.653	1.792	0.845
60	45.2	7.746	1.655	1.778	1.739	0.753
90	51.63	9.487	1.713	1.954	1.685	0.574
120	57.76	10.954	1.762	2.079	1.626	0.481
150	63.81	12.247	1.805	2.176	1.559	0.425
180	71.56	13.416	1.855	2.255	1.454	0.398
210	75.16	14.491	1.876	2.322	1.395	0.358
240	80.26	15.492	1.904	2.380	1.295	0.334
270	86.51	16.432	1.937	2.431	1.130	0.320
300	97.82	17.321	1.990	2.477	0.338	0.326



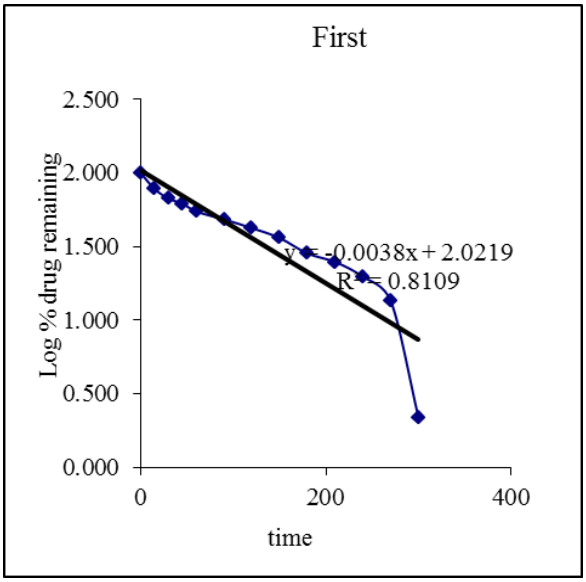
Graph of Zero order release



Graph of higuchi release kinetics



Graph of peppas release kinetics



Graph of first order release kinetics

Drug Release Kinetics Study: The release data analysis was carried out using the various kinetic models i.e. using cumulative % drug release vs. time (zero-order kinetic model); log cumulative % drug remaining vs. time (first-order kinetic model) and cumulative % drug release vs. square 2 roots of time (Higuchi model). The R values are tabulated in the table. All formulae showed best fitting Peppas release kinetics.

CONCLUSION

Emulgel is one of the recent technologies in Novel DDS used for dual control release of emulsion and gel for topical use. Topical drug delivery is generally used to impart better patient compliance. Emulgel helps enhance spreadability, adhesion, and viscosity; hence, this novel drug delivery becomes popular. The rationale of the present study was to increase the penetration of the drug into the skin. In the present investigation, Topical Emulgels of Ethenzamide were formulated and subjected to various physicochemical studies such as spreading coefficient, viscosity, and *in vitro release* studies. *In vitro* release of the test formulations was performed to determine drug release from Gel and Emulgel. From the *in vitro* studies, formulation F9 showed a maximum release of 97.82% in 300 min. So Ethenzamide Emulgel can be used as an anti-inflammatory analgesic agent for topical drug delivery.

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