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EXPLORING THE USE ALKALINE WATER IN DEVELOPMENT OF CARBOPOL BASED DICLOFENAC GEL AND ITS COMPARATIVE EVALUATION

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ABSTRACT

Nowadays, Alkaline water (pH>7) has gained interest by people for better physiological medium. They drink alkaline water in routine daily schedule. It is found to be safe and most accepted by body. Its safe profile can be explored in the various pharmaceutical, cosmetic and food products. The present study was aimed to explore use of alkaline water in formulation of topical Diclofenac gel comprising Carbopol as main gelling agent. Generally, Carbopol exhibits acceptable consistency in alkaline medium. For the sake of providing alkaline medium, selected chemicals (TEA or NaOH) can be added in Carbopol gel to achieve desired consistency. Trials were taken of for developing Carbopol gel using TEA and alkaline water as basicity provider using diclofenac as a model drug. Diclofenac content in formulations was assessed by UV spectrophotometric method at 276 maximum wavelength. The developed formulations and market product (Vollini® gel) were evaluated for various parameters. The results indicated that alkaline water had proven its equivalency with TEA in performance. Similar kind of drug release pattern was obtained. All three formulations including market product have shown Higuchi model as best fit model as far as drug release

kinetics is concerned. The results of accelerated stability study indicate stable characteristics of developed formulations. So, in a nutshell it can be concluded that alkaline water can be used in place of chemicals to provide basicity (TEA/NaoH). The scope of successful use of alkaline water in similar kind of preparations can be increased.

KEYWORDS: Alkaline water, Carbopol gel, Diclofenac, Stability study

1. INTRODUCTION

The act of applying a drug-containing formulation to the skin in order to treat cutaneous illnesses or the cutaneous manifestation of a general disease with the goal of achieving better therapeutic action is known as topical delivery. The system for topical distribution is dominated by semisolid formulations in all of their varieties. Concerns have been raised about the traditional topical dose forms, including gels, in terms of drug distribution through the skin and diffusion or release from the vehicle. With a surface area of 1.7 m^2, the skin is the largest and most accessible organ in the body and accounts for 16% of the average person's total body mass. The primary purpose of the skin is to protect the body from external influences by acting as a barrier against pathogens. Skin can be split into three main areas: the epidermis, the outermost layer, which contains the stratum corneum; the dermis, the middle layer; and the hypodermis, the innermost layer. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.Gels are semisolid systems in which the dispersion medium's mobility is constrained by a three-dimensional network of interlacing particles or solvated macromolecules of the dispersed phase.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic properties that has been shown to be effective in treating a range of acute and chronic pain conditions as well as inflammatory conditions. It is a well-researched, frequently prescribed NSAID. Diclofenac, like all NSAIDs, works by impairing the production of prostaglandins by somewhat equally impairing cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). However, significant research demonstrates that Diclofenac's pharmacologic activity comprises multimodal and, in some cases, new modes of action in addition to COX inhibition (MOA). Diclofenac gel is used to treat pain and other symptoms of arthritis of the joints (eg. Osteoarthritis) such as inflammation, swelling, stiffness, and joint pain.

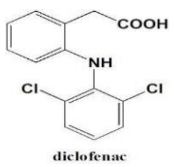


Fig.1:Chemical structure of Diclofenac.

Since many drug substances are weak acids or bases, modifying the pH in topical formulations of these types of compounds may have a significant impact on the degree of ionization, which in turn can have a significant impact on the drug substance's solubility, chemical stability, and lipophilicity. The pH partition hypothesis asserts that an acidic or basic molecule's non-ionized species is more permeable through biological barriers than its ionized species. The pH level of water determines how acidic/alkaline it is and ranges from 0-14. Alkaline water (pH>7) infuses dissolved hydrogen, making water hydrogen rich, 200-300 ppb. Alkaline water declines ORP (Oxidation Reduction Potential), making water antioxidant, and ORP is (-)200 to (-) 500. Alkaline water generates microclustered properties and minerals enriched alkaline water with pH 8.5/9.5.

Alkaline water can neutralize the acidity of the body caused by stress, modern diet, air pollution, and bottled water. Restored body function by cleansing your cells from the inside out. Improves your immune system function to help you fight diseases. A higher pH in the body reduces the need for fat and cholesterol to protect the body from damaging acids. Alkaline water is negatively charged and an “antioxidant”, antioxidants reduces cellular and DNA damage caused by free radicals. High concentration of calcium, potassium, magnesium and sodium which are in ionic state. Alkaline water is thought that drinking water with a higher pH can increase your metabolism and improve your body’s ability to absorb vital nutrients and cancer cells found in your body because cancer cells thrive in an acidic environment.

A "smart gel" is made up by polymer known as Carbopol 934P (C934P), which is mucoadhesive, biodegradable, and environmentally responsive. Allyl ethers of sucrose are used as a cross-linking agent in Carbopol 934P (C934P), which is composed of chains of polyacrylic acid (allylsucrose). As a way to provide an on-off release by contracting and expanding in response to a change in pH, it has recently gained a great deal of interest in the field of drug delivery. By enhancing a drug's *in vivo* stability, the polymer can shield it from its physiological surroundings. Carobopol 934P (C934P) is a non-toxic and non-irritating substance that can be used to prepare gels. To create a proper preparation, one must be concerned with the concentration of Carbopol 934P (C934P), a gelling agent. The benefits of using alkaline water are to provide the natural source of pH so that we don't need to use NaOH or Triethanolamine (TEA) for changing pH of any pharmaceutical formulation. Carobopol 934P (C934P) will relax the chain when mixed with any alkaline agent and gives the optimum output. Secondly, alkaline water is more readily accessible and less expensive than NaOH or Triethanolamine (TEA).

Thus, the present study was aimed to employ alkaline water in formulation of Carbopol to provide basic environment in place of NaOH or TEA. The developed formulations including market product were evaluated for different physical and performance indicating parameters and compared.

2. MATERIALS AND METHODS

2.1 Materials

Diclofenac was purchased from Redson pharmaceuticals, Ahmadabad, India. Carbopol 934P was procured from Finechem PVT. LTD., Bangalore. Alkaline water was taken from the Enagic Kangen Water machine , model: Leveluk SD501, Osaka, Japan. Ethanol was procured from Canadian pharma, Shahin park, Ahmedabad. Triethanolamine was purchased from Panchamrut chemical, Mumbai-Borivali West. Methyl paraben powder was collected from Varcas pharmaceuticals, Ahmedabad. Propyl paraben powder was collected from Akhil Healthcare PVT. LTD, Vadodara. Marketed formulation (Diclofenac gel 30 gm) was purchased from Shree Uma Medical store, Ahmedabad.

2.2 Methods

2.2.1 Quantification of Diclofenac

An UV-visible spectrophotometer was used to scan Diclofenac using ethanol (Shimadzu UV-1800). A stock solution of Diclofenac was checked for absorbance between 200 to 800 nm ranges (Shimadzu UV- 1800). Ethanol was used as a control at 276 nm , diclofenac exhibits its peak UV absorption. 100 mg Diclofenac drug powder was dissolved in 100 ml ethanol to create a stock solution with a 1000 µg/ml concentration. (Stock-1), From the above stock 1,1.5,2,2.5,3 and 3.5 ml of the solution were taken and transferred to a 10 ml volumetric flask, where the capacity was then filled with ethanol to achieve a concentration of 100-350 µg/ml.

(A) Preparation of Phosphate buffer pH 6.8 : 28.20 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogenphosphate dissolved in sufficient water to produce 1000ml. Stock solution (100 µg/ml) was prepared by adding 5 mg Diclofenc drug in 50ml of phosphate buffer solution. Prepared stock solution was further diluted with PBS to make different concentration like 5,10,15,20,25 and 30 µg/ml. Then using UV spectrophotometer absorbance was taken at 276 nm (ʎ max of Diclofenac)(3).

(B) Preparation of standard calibration curve in Diclofenac:

In analytical chemistry, a calibration curve is a general method for determining the concentration of a substance in an unknown sample by comparing the unknown to a set of standard sample of known concentration. In spectrophotometric analysis a series of standard solution of known concentration are prepared and absorbance is measured using spectrophotometer instrument to determine the unknown concentration of sample by Beer's law. A calibration is a graph where concentration is plotted against absorbance then a straight line (Beer's law) is fit to the data that we obtained and the resulting equation is used to convert absorbance of the unknown sample into concentration.

2.2.2 Preliminary trials:

(A) Solubility of Diclofenac drug powder: To check the solubility of Diclofenac drug powder, Diclofenac drug powder was dissloved in two beaker (Beaker A and Beaker B). Beaker A containing 1% (1gm) Diclofenac drug powder in 100 ml distilled water. Beaker B containing 1% (1gm) Diclofenac drug powder in 100 ml alkaline water (pH-9) and it was observed for few minutes .

(B) Procedure of the gel formation with different pH of water : Carbopol 934P (C934P) was tested with the total 6 different pH of the water Carbopol 934P (C934P)was measured accurately about 0.1 mg and and then added into the 5 ml of alklaine water of different pH like 2.5,6.0,7.0,8.5,9.0 and 9.5 and it was observed for 24 hours.

2.2.3 Preparation of Diclofenc gel

(A) Preparation of distilled water containing Diclofenc 1% gel: About 1 gm of Diclofenac was weighed and dissolved in 10 ml of ethanol to this solution, specified quantity of propylene glycol (5ml) was added and dissolved (solution A). Weighed quantity of polymer Carbopol 934 P (1.5 gm) was added to sufficient amount of distilled water, mix uniformity by using magnetic stirrer(solution B). Solution A and solution B were mixed thoroughly to that Triethanolamine was added with continuous stirring and then added 0.5% of methyl paraben and 0.5% of propyl paraben as a preservative.

(B) Preparation of alkaline water containing Diclofenac 1% gel: About 1 gm of Diclofenac was weighed and dissolved in the 100 ml of alkaline water (pH- 9),and then specified quantity of propylene glycol (5ml) was added and dissolved (solution A). Weighed quantity of polymer Carbopol 934P (1.5gm) was added to sufficient amount of alkaline water (pH-9) ,mix uniformity by using magnetic stirrer(solution B). Solution A and solution B were mixed thoroughly to that and then added 0.5% of methyl paraben and 0.5% of propyl paraben as a preservative.

2.2.4 Characterization of drug loaded gel and Alkaline water containing gel (4,5)

(A) pH

The pH of Diclofenac 1% gel was measured by using digital pH meter. The results are shown in Table 1.

(B) Spreadibility

An ideal topical gel should possess a sufficient spreading coefficient when applied or rubbed on the skin surface. This was evaluated by placing about 1 g of formulation on a glass slide. Another glass slide of the same length was placed above that, and a mass of 500g was put on the glass slide so that the gel gets sandwiched between the two glass slides and spreads at a certain distance. The time taken for the gel to travel

the distance from the place of it's position was noted down. Spreadibility was determined by this following formula.

$$S = \frac{M * L}{T}$$

Where, S- Spreadability, g.cm/s

M- Weight put on the upper glass

L- Length of glass slide

T- Time for spreading gel in sec. And the results are shown in the Table 1.

(C) Extrudability

Extrudability test was carried out by using Pfizer hardness tester. 15 gm of gel was filled in collapsible aluminium tube. The plunger was adjusted to hold the tube properly the pressure and applied. The quantity of the gel extruded was weighed. The procedure was repeated at three times. The results are shown in Table 1.

(D) Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. The results are shown in Table 1.

(E) Viscosity

Viscosity was determined by using brookfield viscometer. Viscosity measurements were carried out at room temperature(25-27˚c) using a brookfield viscometer(model RVTDV II). The results are shown in Table 2.

(F) Clarity

Clarity of various formulation was determined by visual inspection under black and white background and it was graded as follows : turbid(+), clear(++), very clear (glassy)(+++). The results shown in Table 2.

(G) Drug content

A specific quantity (100mg) of developed gel and marketed gel were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was taken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated

spectrophotometrically at 276 nm using phosphate buffer (pH 6.8) as blank. The results are shown in Table 2.

(H) *In-vitro* drug release study

Phosphate buffer of pH 7.4 was used for *in vitro* release as a receptor medium. The pretreated artificial cellulose membrane(0.45 µm) was used in fraz diffusion cell. The gel sample was applied on the artificial cellulose membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer (100ml) of pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37˚C± 1˚C by surrounding water in jacket and the medium was stirred by magnetic stirrer at 100rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid (6,7) . The samples withdrawn were spectrophotometrically estimated at 276 nm against their respective blank. The results are shown in Table 3.

Fig.2 : Franz diffusion cell

2.2.5. Accelerated stability studies

All the selected formulation were subjected to a stability testing for three months as per ICH norms at a temperature 40˚c ± 2˚C/RH. All selected formulations were analyzed for the change in appearance, pH or drug content by procedure stated earlier (8–10) . The results are shown in Table 4.

3. RESULT AND DISCUSSION

The objective of the present study was to formulate transdermal gel of Diclofenac using Carbopol 934P as a selling polymer and alkaline water as basic vehicle. In order to select the optimized formulation, various evaluation parameters were checked.

3.1 Quantification of Diclofenac

The quantification of Diclofenac was done in UV and the liner range was found to be 100-350 mcg/mL. The calibration equation was found to be Y= X + C (Y=0.023X+0.011). This linear regression equation was employed in further study for quantification for Diclofenac.

3.2 Preliminary trials:

(A) Solubility with different pH of water

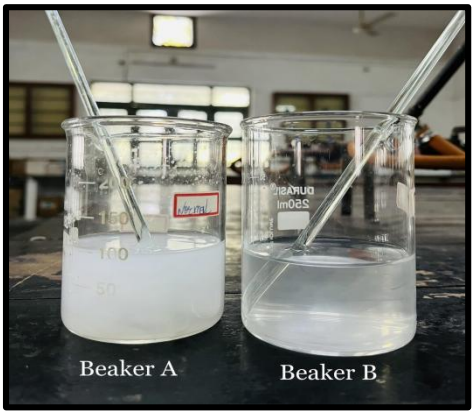


Fig.3: Solubility with different pH of water

Significant improvement in solubility of Diclofenac was observered when Diclofenac was solubilized in alkaline was (pH-9) realative to normal water. This infero that, in any preformulation study of formulation of Diclofenac, alkaline water must be added. Further, alkaline water can be a best choice for solubility of Diclofenac and similar drugs. The remarkable difference in solubility of Diclofenac can be observed in fig.3.

(B) Carbopol 934P with different pH of water

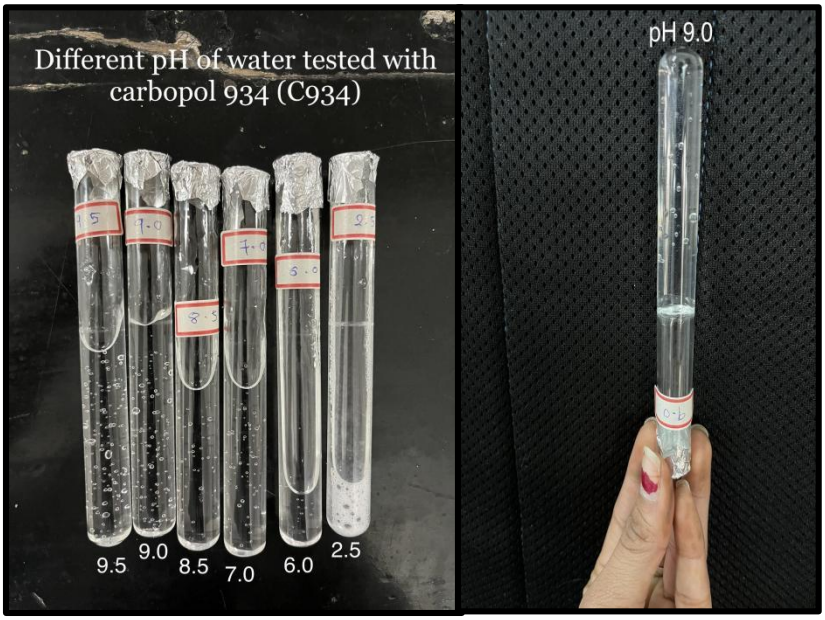


Fig.4: Carbopol 934P with different pH of water

In fig.4 Carcopol 934P (C934P) was tested with the different pH of water. Chemical nature of C934P is acidic and most of the study indicates that when Carbopol 934P (C934P) is mixed with the any alkaline substance (e.g., NaOH/TEA), it converts into gel form. Here, Carbopol 934P (C934P) was tested with six different samples of alkaline water having pH 2.5, 6.0, 7.0, 8.5, 9.0 and 9.5. Result of this study (fig.3) indicates that C934P gives the best gel formation with the pH-9. Thus, further experimentation was conducted with the pH-9 alkaline water. The consistency of Carbopol solution was found to be increased as the pH was increased on higher side. This indicates that higher pH(around 9) is a favourable condition for Carbopol to convert into gel.

3.3 Developed Diclofenac gel

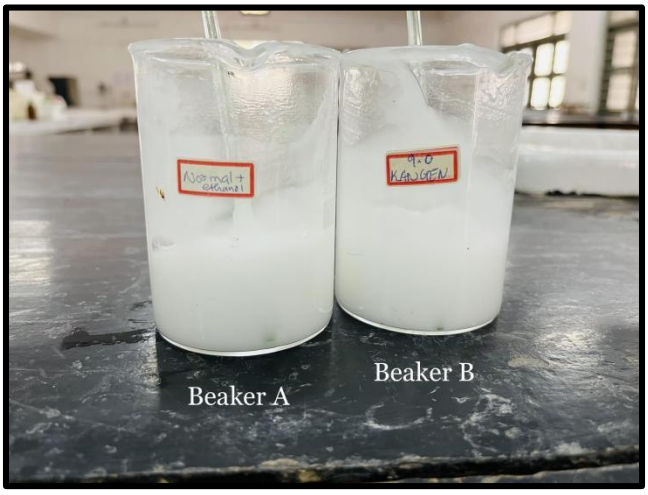


Fig.5: Developed Diclofenac gel

Diclofenac gel was successfully developed using normal distilled water with TEA (Beaker-A) as alkalinity provider and alkaline water without TEA (Beaker-B). There was no any remarkable difference in the consistency ,appearance, pH, texture and viscosity of formulations developed with TEA and without TEA. The results are shown in the fig.5.

3.4 Characterization

(A) pH

The pH value of the normal Diclofenac 1% gel was found to be 6.8±0.2 and pH value of alkaline water containing Diclofenac 1% gel was 6.7±0.2. The pH value of the marketed gel was 6.8±0.1. It is concluded that all the formulations have pH almost neutral which confirm the suitability of products for topical application without any sign of skin irritation. The results of pH are shown in Table 1.

(B) Spreadibility

The value of Spreadibility indicates that the gel is easily spreadable by small amount of shear. In normal Diclofenac 1% gel, Spreadibility was found to be 7.0±0.2 g.cm/sec, whereas that of in alkaline water containing Diclofenac 1% gel it was 7.5±0.2 g.cm/sec. The Spreadibility of marketed Diclofenac gel was 8.0±0.2 g.cm/sec. It indicates that the Spreadibility of the normal and alkaline water containing gel was equivalent to marketed gel. The results are shown in Table 1.

(C) Extrudability

When applying the gel and ensuring that the patient accepts it, the extrusion of the gel from the tube is crucial. High consistency gels might not extrude from the tube. In contrast, low viscosity gels may flow quickly; as a result, the gel must have the right consistency to be extruded from the tube. The results are shown in Table 1.

(D) Homogeneity

All developed gels showed good homogeneity without any lumps. The developed preparations were much clear and transparent. The results are shown in Table 1.

Table 1: pH, Spreadibility, Extrudability and Homogeneity

Formulation	**pH**	**Spreadibility (g.cm/sec)**	**Extrudability**	**Homogeneity**
Normal diclofenac 1% gel	6.8±0.2	7.0±0.2	Good	Good
Alkaline water containing diclofenc 1% gel	6.7±0.2	7.5.±0.2	Good	Good
Marketed gel	6.8±0.1	8.0 ±0.2	Good	Good

(E) Viscosity

The viscosity of the normal Diclofenac 1% gel was 3,19,800 cps. The alkaline water containing Diclofenc 1% gel was found as a 3,19,600 cps. The viscosity of the marketed gel was 3,20,000cps. The viscosity of developed formulation were almost equivalent. The results are shown in Table 2.

(F) Clarity

Normal Diclofenac 1% gel, alkaline water containing Diclofenac 1% gel and marketed gel was found to be clear. All gels were free from presence of particles. The results are shown in the Table 2.

(G) Drug content

The percentage drug content of all developed gel formulations was found in the acceptable range as per the I.P. The results are shown in the Table 2.

Table 2: Viscosity, Clarity and Drug content

Formulation	**Viscosity(cps)**	**Clarity**	**Drug content(%)**
Normal Diclofenac 1% gel	3,19,800	Clear	99.70±0.25
Alkaline water containing Diclofenc 1% gel	3,19,600	Clear	98.80±0.31
Marketed gel	3,20,000	Clear	99.90±0.18

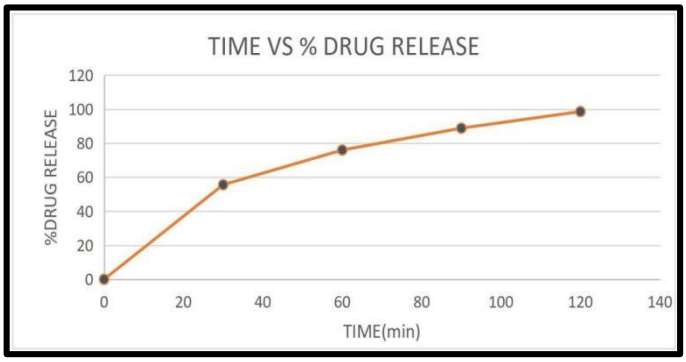
(H) *In-vitro* drug release study

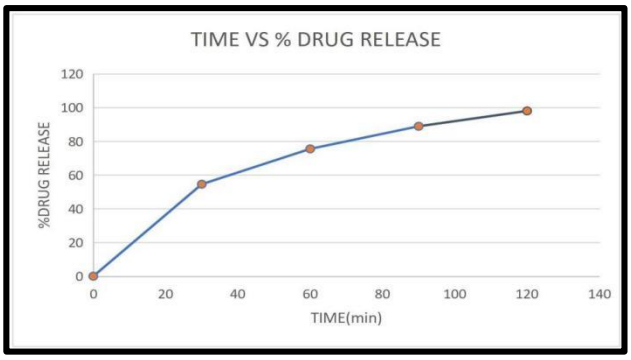
The percentage drug released after 2 hours was found to be 98.00% from alkaline water containing gel. Similar amount of % drug released was found for normal Diclofenac gel(98.60%) and marketed gel (98.66%). These indicates that there were insignificant differences in released amount for developed formulation. This means alkaline water doesn't causes any impact on drug release pattern. The results are shown in the Table 3.

Table 3: % drug release study for normal gel , alkaline water containing gel and marketed gel

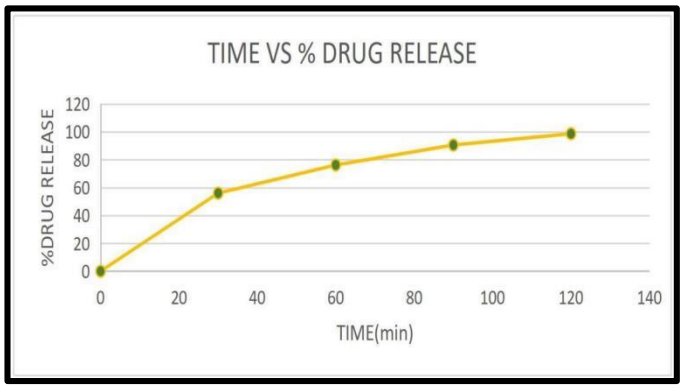
Sr.no	**Time interval (min)**	**Medium pH**	**% drug release**		
			Normal Diclofenac 1% gel	Alkaline water containing Diclofenac 1% gel	Marketed gel
1	30	6.8	55.60	54.55	56.00
2	60	6.8	76.00	75.50	76.20

3	90	6.8	88.85	88.90	90.55
4	120	6.8	98.60	98.00	98.66





%drug released from normal Diclofenac gel % drug released from alkaline water containing gel(pH-9)



3.5 Accelerated stability study

The results of accelerated stability study are depicted in Table 4. All formulation shared stable characteristics after stipulated time of stability study. There were no any significant of insolubility and any indication of microbial growth.

Table 4: Accelerated stability study of normal gel, alkaline water containing gel and marketed gel

Sr.no	Batches	Time interval (month)	Apperance	pH	Drug content(%)
1		0	Clear	6.8	99.75

	F1 (normal Diclofenac Gel)	1	Clear	6.8	98.56
		2	Clear	6.7	97.95
		3	Clear	6.6	99.70
2	F2 (alkaline containing Diclofenc 1% gel)	0	Clear	6.8	99.94
		1	Clear	6.8	98.50
		2	Clear	6.7	95.60
		3	Clear	6.5	96.30
3	Marketed gel	0	Clear	6.8	99..95
		1	Clear	6.7	98.10
		2	Clear	6.6	97.60
		3	Clear	6.5	97.50

CONCLUSION

Taking together the results of presented study, it can be concluded that alkaline water (pH-9) can be a strong replacement of any chemical which are added to impart alkaline environment in formulations. The drug released pattern and other physicochemical parameters were unaffected by alkaline water. In a nutshell, it can be concluded that alkaline water with selected pH can be used in pharmaceutical preparations where basic pH is needed (e.g. Gel formulations) to provide basicity.

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