ejpmr, 2023, 10(5), 346-360

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STUDIES ON EFFECT OF ALOEVERA GEL ON THE RELEASE PROFILE OF DICLOFENAC POTASSIUM FROM DIFFERENT FORMULATIONS

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Article Received on 03/03/2023 **Article Revised on 23/03/2023** **Article Accepted on 13/04/2023**

ABSTRACT

A sustained release formulation is one which delivers the drug slowly and continuously for an extended period of time. Diclofenac Potassium is a non-steroidal anti-inflammatory agent with short half life and undergoes first pass metabolism with a bioavailability of 50%, hence suitable for developing sustained release formulation. From the review of literature, it was found that aloevera gel powder is a potential drug release retardant. The aim of this research work was to formulate an optimized sustained release tablet of Diclofenac Potassium using aloevera gel powder as the release retardant. The formulations were designed as suggested by the design expert software (version 13, Stat- Ease) using aloevera gel powder (AGP) & hydroxyl propyl methyl cellulose(HPMC) as the release retardants along with other excipients by direct compression method. The formulated tablets were of uniform weight and drug content. The pharmaceutical properties of all formulations and their *invitro* drug release were evaluated. The optimized formulation, F6 showed a drug release of 100% at the end of 12 hours & followed first order kinetics with non fickian release pattern. From the drug release profile, it was observed that aloevera gel powder had a retardant effect. Hence it can be concluded that aloevera gel powder is a potential and economical drug release retardant for the development of sustained release dosage form.

KEYWORDS: Aloevera gel powder, Diclofenac potassium, Sustained release tablet.

1. INTRODUCTION

The oral route of drug administration is the most effective and widely used method of drug delivery because of its high patient compliance, cost-effectiveness, flexibility in the design of dosage form and ease of production.[1] But conventional dosage form offers few limitations such as poor patient compliance, chances of dose missing, see-saw fluctuations, risk of toxicity as well as overall cost of treatment. Development of new, better and safer drugs with long half-life and large therapeutic indices, effective and safer use of existing drugs through concepts and techniques of controlled and targeted drug delivery systems can overcome these limitations. An ideal controlled drug delivery system is the one which delivers the drug at a specific rate locally or systemically for a specified period of time with minimum fluctuation in plasma drug concentration, reduced toxicity and maximum efficiency.[2]

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms due to its simple processing and a low cost of fabrication. They can be prepared in two ways, one is direct compression of the powder blend containing the drug, polymer and other additives, and another one involves granulation prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients.[3]

Aloe vera (L.) (Aloe barbadensis Miller) is a perennial succulent xerophyte, which develops water storage tissue in the leaves to survive in dry areas of low or erratic rainfall. A.vera has been used for many centuries for its curative and therapeutic properties. In the pharmaceutical industry, it has been used for the manufacture of topical products such as ointments and gel preparations, as well as in the production of tablets and capsules. Due to its absorption enhancing effects, A.vera gel may be employed to effectively deliver poorly absorbable drugs through the oral route. Furthermore, the dried powder obtained from A.vera gel was successfully used to manufacture directly compressible matrix type tablets. These matrix type tablets slowly released a model compound over an extended period of time and thereby showing potential to be used as an excipient in modified release dosage forms.[4]

Diclofenac potassium is an NSAID with short half-life of 1.2-2hrs, and undergoes first pass metabolism such that

only 50-60% of administered dose reaches the systemic circulation, hence it is a suitable drug for developing a sustained release formulation. From literature review it is evident that aloevera has the potential to retard the release of a drug from its dosage form. Hence this study is aimed to develop an optimized formulation of sustained release tablet of diclofenac potassium using aloevera gel as release retarding agent.

The main aim of this study is to determine the effect of aloevera gel powder on the release profile of diclofenac potassium from different tablet formulations. The study on the effect of aloevera gel powder on HPMC is the value addition in this research. Hence sustained release tablets were prepared using aloevera gel powder alone and in combination with HPMC.

2. MATERIAL AND METHODS

Materials

2.1. Chemicals used

Diclofenac potassium (Yarrow Chem Products, Mumbai), Aloevera gel powder (H&C Naturals Mumbai), HPMC (Lobo Chemie, Mumbai), Micro Crystalline Cellulose/MCC (Sisco research laboratories, Maharashtra), Magnesium stearate (Thomas baker Mumbai), Aerosil (Isochem laboratories, Kochi), Talc (Sd fine- Chem Ltd, Mumbai), Hydrochloric acid (Finar, Ahmedabad).

2.2. Instruments used

Double beam UV Spectrophotometer (Systronics, UV-VIS Spectrophotometer117, Ahmedabad), FT-IR (Jasco model FT/IR 4100), DSC (TA instruments model Q20), 10 station rotary tablet punching machine (Multispan, Ahmedabad), Dissolution apparatus (Electro lab, Mumbai), Electronic weighing balance (Prince scale industries, Ahmedabad), Friabilator (Roche friabilator), Pfizer hardness tester (Rolex, Haryana), Bulk density apparatus (Labtech, Mumbai).

Methods

Preformulation Study

Preformulation studies is the type of study that focus on the various physicochemical properties of drug sample that may affect the performance of drug and development of dosage form. It is the first step in dosage form development. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing. All these can affect the characteristics of blends produced. The main purpose of preformulation studies is to develop the stable, effective and safe dosage form by establishing kinetic rate profile and compatibility with other excipients.[5]

2.3. Analytical Methods

2.3.1. Determination of UV λ max

2.3.1.1. UV absorption spectrum of Diclofenac potassium in 0.1N HCl

Dissolve accurately weighed 100 mg of Diclofenac potassium in 100 ml of 0.1N HCl of pH 1.2 in 100ml standard flask to get 1mg/ml solution. From the stock solution of Diclofenac potassium, 1ml is pipetted out and diluted to 100ml with methanol to get 10µg/ml. The absorption maximum of standard solution of Diclofenac potassium is determined by scanning the resulting stock solution in UV spectrometer at 200 - 600 nm. The absorption maxima obtained is compared with reference standard for the value.

2.3.1.2. UV absorption spectrum of Diclofenac potassium in 6.8 pH Phosphate buffer

Similar to the above procedure except that 6.8 pH Phosphate buffer is used in place of 0.1N HCl.

2.3.2. Calibration curve construction.

2.3.2.1 Preparation of Standard Calibration Curve of Diclofenac potassium in 0.1N HCl

In a 100 ml volumetric flask, standard solution was prepared by dissolving 100 mg of Diclofenac potassium in 0.1N HCl and made up to the volume with 0.1N HCl. From the standard solution, 1 ml was taken and the volume was made up to 100 ml with distilled water and it was labelled as stock. From this stock solution, serial dilutions were made by withdrawing 2ml, 4ml, 6 ml, 8 ml and 10 ml and transferred individually into 10 ml standard flask and the volume was made up to the mark using 0.1N HCl. The absorbance of the samples was observed using UV spectrophotometer at a wavelength of 276 nm and a graph is plotted between concentration taken on x- axis and absorbance taken on y-axis.

2.3.2.2 Preparation of Standard Calibration Curve of Diclofenac potassium in 6.8 Phosphate buffer

Similar to above procedure except that 6.8 phosphate buffer is used in place of 0.1N HCl.[6]

2.4 Physicochemical properties of drug

2.4.2 Organoleptic evaluation

The pure drug obtained was evaluated for various organoleptic properties such as nature, colour, odour, hygroscopicity, crystallinity etc**.**

2.4.3 Determination of melting point by capillary method

A small amount (0.1-0.2g) of pure drug was transferred onto a watch glass. One end of capillary tube of 5cm long was sealed and the solid was introduced into a capillary tube and packed to a height of 3 cm. Then the capillary tube was placed in melting point apparatus and the temperature at which the melting of drug started was noted by using the thermometer placed in the apparatus.[6]

2.4.4 Solubility study

The saturation solubility study was carried out to determine the solubility of pure Diclofenac Potassium. Excess amount of drug was added to 250 ml conical flasks containing 100 ml of solvent and the flasks were subjected to shaking using rotary shaker. Then, the aliquots were withdrawn and filtered through whatmann filter paper. The absorbance of samples was determined by UV spectrophotometer at 276 nm. Solubility of Diclofenac potassium was observed in different solvents such as distilled water, 95% ethanol, 0.1N HCl (pH 1.2), Phosphate buffer (pH 6.8), chloroform & ether. Solubility was calculated using the formula.[6]

Solubility= (absorbance of sample/absorbance of standard solution) × concentration of standard solution × dilution factor

2.4.5 Determination of flow properties of aloevera gel powder

The flow properties of aloevera gel powder was determined using angle of repose, Carr's index and Hausner's ratio values.

2.4.6 Drug –Excipient compatibility

FTIR spectroscopic method was used for carried out drug-excipient compatibility study. FT-IR spectra of pure drug, aloevera gel powder, HPMC and their physical mixtures were taken by KBr pellet technique between 400–4000cm^{-1}. Once spectra was recorded, the peaks of pure drug, polymers and physical mixtures of polymers and drug were compared for incompatibility.

2.5 Precompression parameters of powder blends

2.5.2 Bulk density and Tapped density

10gm of powder was weighed. Weighed amount of given powder was introduced into measuring cylinder attached with bulk density apparatus. After that the initial volume was observed for bulk density and then cylinder was tapped continuously until no further change in volume was observed. Record the final volume for tapped density. Then bulk and tapped density were calculated by using the given formula.

Bulk density = Weight of powder ÷ Initial volume

Tapped density = Weight of powder÷Tapped volume

2.5.3 Carr's index[7]

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indicated as Carr's compressibility index (CI) and can be calculated as follow:

$$\text{Carr's index (\%)} = \frac{\text{(tapped density) - (bulk density)} \times 100}{\text{(tapped density)}}$$

2.5.4 Hausner's ratio[7]

Hausner's ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the bulk density. Hausner's ratio is calculated as:

Hausner's ratio = Tapped density ÷ Bulk density

2.5.5 Angle of repose

Maximum angle possible between the surface of a pile of powder and the horizontal plane are referred as angle of repose. Angle of repose is used to measure the frictional force leads to improper flow. Fixed funnel method was used for determining the angle of repose. The average value was taken and angle of repose was calculated by using the given equation.

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

Where θ = Angle of repose, h = height of the heap, r = radius of the heap

2.6 Compression of Tablet

Technology Applied: Direct compression

The direct compression method was used for the formulating the sustained release tablet of the Diclofenac Potassium using the natural polymer aloevera gel powder& synthetic polymer HPMC. The Diclofenac Potassium, Aloevera gel powder, HPMC & MCC were mixed and passed through the 40# sieve. Afterward magnesium stearate and aerosol was added and mixed to it[8] Final mixture was compressed on the multi-station rotary tablet compression machine

The key ingredients included in the formulations are.

API: Diclofenac potassium

Release retarding Polymers: HPMC and Aloevera gel powder

Diluent: Micro Crystalline Cellulose

Glidant: Aerosil

Lubricant: Magnesium Stearate.

Design Expert (Version 13.0.7.0, Stat- Ease) Software was used to design formulations. Thirteen formulations with variable concentrations of release retarding polymers i.e. AGP & HPMC were suggested by the software. The formulation design is shown in table 1.

Table no. 1: Formulation table for Diclofenac Potassium sustained release tablet using aloevera gel powder and HPMC as release retardants.

Formulation code and composition (mg/tab)							
Formulation	**DFP**	**AGP**	**HPMC**	**MCC**	**Magnesium stearate**	**Aerosil**	**Total weight**
F1	100	40	70	185	3	2	400
F2	100	0	70	225	3	2	400
F3	100	40	70	185	3	2	400
F4	100	80	140	75	3	2	400

F5	100	0	140	155	3	2	400
F6	100	80	70	145	3	2	400
F7	100	40	70	185	3	2	400
F8	100	0	0	295	3	2	400
F9	100	80	0	215	3	2	400
F10	100	40	70	185	3	2	400
F11	100	40	0	255	3	2	400
F12	100	40	70	185	3	2	400
F13	100	40	140	115	3	2	400

2.7 Post Compression Parameter (Evaluation)

The prepared tablets were evaluated for general appearance, hardness, friability, weight variation, In vitro dissolution studies, and short-term stability study.

2.7.2 Physical properties of sustained release tablets[3]

The tablets were characterized immediately after the formulation. The weight variation of the 20 tablets was accomplished according to guidelines mentioned in I.P. 1996 using an electronic balance. Friability of 10 tablets was evaluated by Roche type friabilator for 4 min at the rate of 25 rpm and calculate using the formula,

$F = (1- W/ W_0) \times 100$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

For each formulation the hardness of 10 tablets was evaluated using Monsanto hardness tester. As the formulations are meant for sustained release there is no scope for disintegration test.[9] The drug content was determined by taking accurately weighed amount of powdered Diclofenac Potassium tablets (equivalent to 100 mg of Diclofenac Potassium) & extracted with pH 6.8 buffer and the solution was filtered. The absorbance was measured at 276 nm after suitable dilution.

2.7.3 *In vitro* dissolution studies

The dissolution studies were performed in triplicate for all the batches in a USP dissolution test apparatus (Type I). The release studies were performed at 50 rpm in 900 ml of 1.2 pH buffer at 37± 0.2^0C for first 2 hours and replaced with phosphate buffer of pH 6.8 for further studies. Aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh pre-warmed dissolution medium. The absorbance of the withdrawn samples was measured spectrophotometrically at 276 nm and the percentage drug release calculated was calculated.

2.8 Optimization of sustained release formulation by response surface methodology (RSM)

2.8.2 Experimental design

The optimization of Sustained release formulation of was done by using the design expert software (Design Expert software statease version 13). A central composite design (CCD) with a 2 factor and 3 levels were used. Based on preformulation study the amounts of AGP (X1) and HPMC (X2) were selected as the independent factors, studied at three levels each. The central point (0,0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 3 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. % of drug released in 2 h (Y1), % of drug released in12 h(Y2), time for 50% drug release ($t_{50\%}$) (Y3) were taken as the response variables.

Table no. 2: Factor combination by CCD for formulation of diclofenac potassium (400mg) tablets.

Formulation code	Point type	Coded Factor Level	
		X1	X2
F1	Factorial	-1	-1
F2	Factorial	+1	-1
F3	Factorial	-1	+1
F4	Factorial	+1	+1
F5	Axial	-α	0
F6	Axial	+α	0
F7	Axial	0	-α
F8	Axial	0	+α
F9	Central point	0	0
F10	Central point	0	0
F11	Central point	0	0
F12	Central point	0	0
F13	Central point	0	0

Coded level	-1	0	+1
X1, amount of AGP	0	40	80
X2, amount of HPMC	0	80	140

2.9 Analysis of kinetics and mechanism of drug release

The dissolution data were fitted into the different drug release kinetic models (zero order, first order, Higuchi and Korsmeyer–Pappas model) to evaluate the rate and mechanism of drug release from the matrix tablets. The order and mechanism of drug release from the matrix system were determined based on regression (R^2) values.

2.10 Statistical analysis

One-way analysis of variance (ANOVA) was applied for comparison of results. To demonstrate graphically the influence of each factor on responses and to indicate the optimum level of factors, the contour and response surface plots were generated using Design-Expert software (Stat-ease, 13). At 95% confidence interval, p-values of < 0.05 were considered statistically significant. All the data measured and reported were averages of a minimum of triplicate measurements and the values are expressed as mean ± standard deviation.[1]

2.11 Stability studies

This study was carried out at temperature and humidity conditions as per ICH guidelines and the tests were carried out in a stability chamber.[9] The temperature and humidity conditions used were, 40ºC ± 2ºC at 75% ± 5% RH, 25ºC ± 2ºC at 60% ± 5% RH, 5ºC ± 3ºC.Samples were withdrawn at 0 day, 30 days and 90 days time intervals and evaluated for hardness, friability, drug content, and *in vitro* drug release.

3 RESULTS AND DISCUSSION

3.3 Analytical method

3.3.2 Determination of UV λ max

The pure drug of Diclofenac Potassium was scanned by UV spectroscopy and λmax was found to be 276 nm.

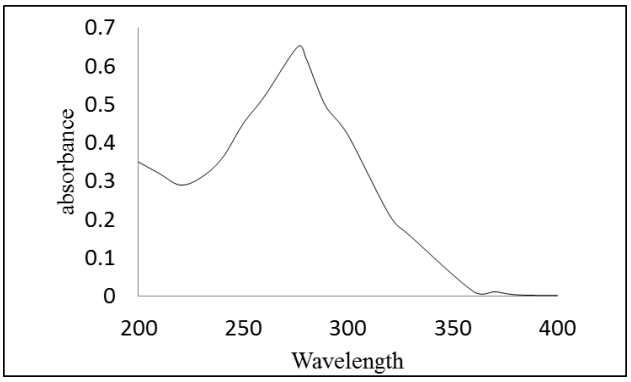

Fig. no. 1: Absorption maxima of Diclofenac Potassium in 0.1N HCl.

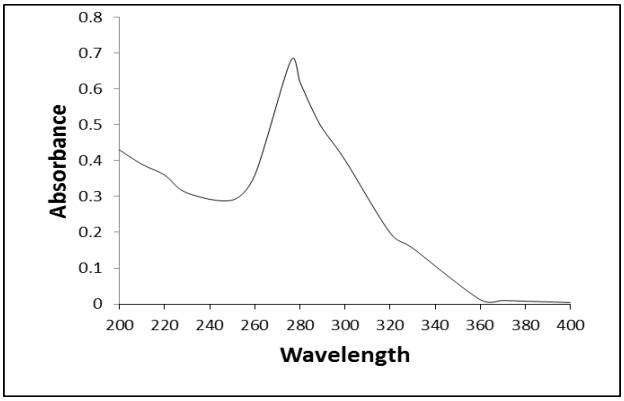

Fig. no. 2: Absorption maxima of Diclofenac Potassium in Phosphate buffer pH 6.8.

3.3.3 Calibration curve of diclofenac potassium

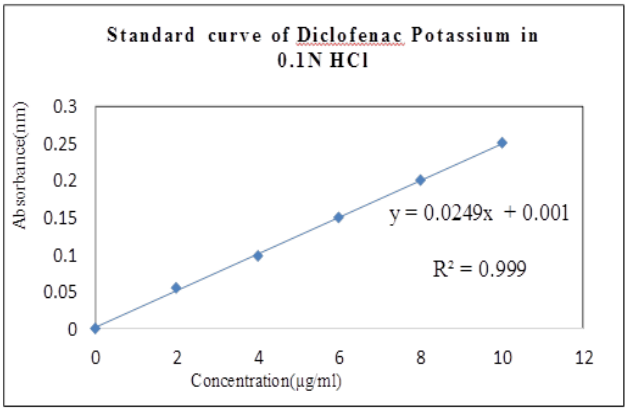

Figure no. 3: Standard curve of diclofenac potassium in 0.1N HCl at 276nm.

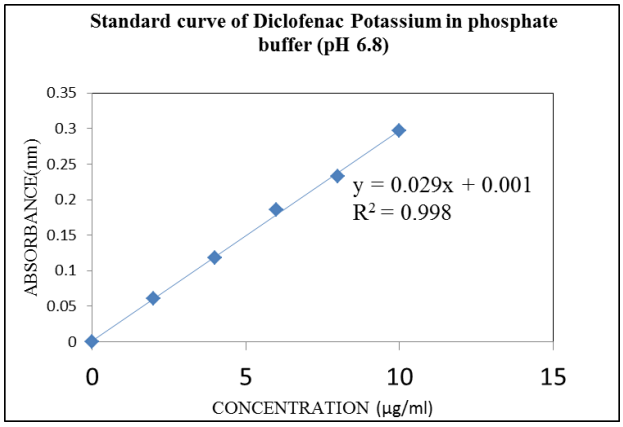

Figure no. 4: Standard curve of diclofenac potassium in phosphate buffer (pH 6.8) at 276nm.

The drug was scanned in UV region (200-600 nm) by preparing 1mg/ml solution using 0.1N HCl of pH 1.2 as well as phosphate buffer pH 6.8 to find out wavelength of maximum absorption (λ max). The λmax was found to be 276 nm. So the standard calibration curve of diclofenac potassium was developed at this wavelength. Standard calibration curve of diclofenac potassium was determined in 0.1N HCl of pH 1.2 & phosphate buffer pH 6.8 by plotting absorbance against concentration at 276 nm. The calculation of drug content, in vitro drug release and stability studies are based on this calibration curve.

3.4 Physico-chemical properties of drug

3.4.2 Organoleptic properties

Organoleptic properties of diclofenac potassium was studied and it was concluded that diclofenac potassium, is a white or slightly yellowish slightly hygroscopic crystalline powder, odourless & slightly bitter in taste.

3.4.3 Determination of melting point

Melting point was determined by capillary rise method and it was found to be 284 ± 3.05°C (n=3), which complies with the official standards.

3.4.4 Solubility profile

Solubility studies were carried out in different solvents such as distilled water, 95% ethanol, methanol, 0.1N HCl (pH 1.2), phosphate buffer (pH 6.8), chloroform &ether and the results are indicated in table 3.

Table 3: Solubility profile of the diclofenac potassium in different solvents.

Name of the media	Saturation solubility of drug
Water	Sparingly soluble
Acetone	Slightly soluble
Methyl Alcohol	Freely soluble
0.1 N HCL	Very Slightly soluble
Phosphate buffer (pH 6.8)	soluble
Chloroform & Ether	Insoluble

3.4.5 Determination of flow properties of aloevera gel powder

Table 4 shows the results of flow properties of aloevera gel powder and is found to have good flow property.

Table no. 4: Flow properties of aloevera gel powder.

Sl. No.	Parameters	Value
1.	Bulk density (g/ml)	0.33 ± 0.012
2.	Tapped density (g/ml)	0.38 ± 0.014
3.	Carr's index(%)	13.15 ± 0.06
4.	Hausner's ratio	1.15 ± 0.0012
5.	Angle of repose(^{0})	22.3^0 ± 0.456

Allvalues are expressed as mean ± standard deviation, n=3

3.4.6 Drug-Excipient compatability studies

3.4.6.1 FTIR spectroscopy

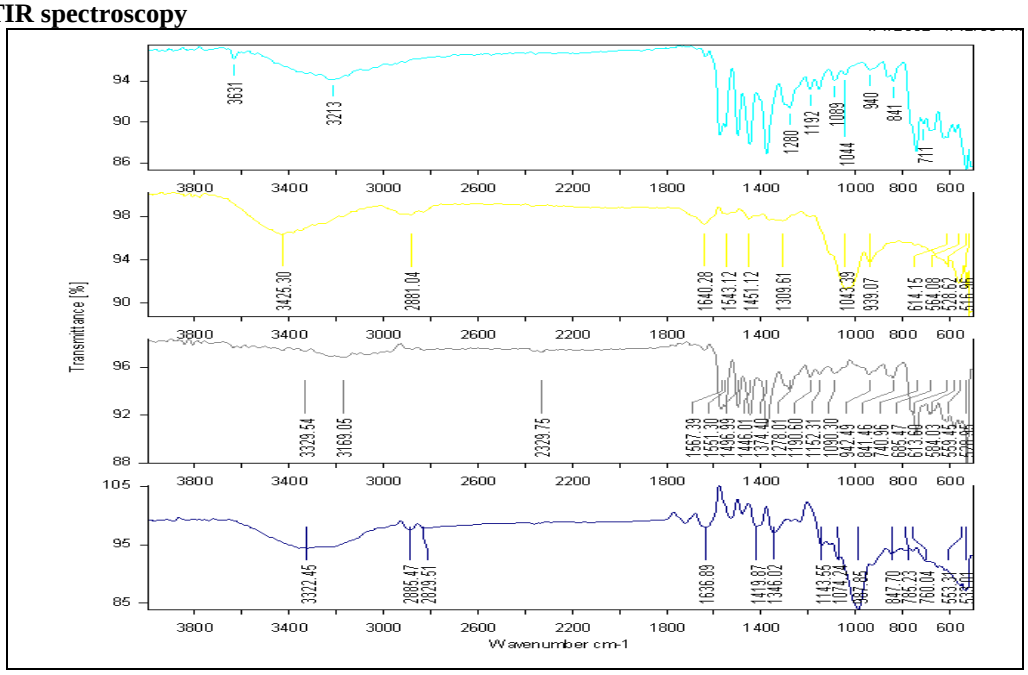

Fig. no. 5: FTIR spectrum of diclofenac potassium, aloevera gel powder, HPMC, and Their combination.

Drug identification was done by performing FT-IR studies. During FT-IR studies, the peaks of diclofenac potassium was obtained at 3213cm^{-1} (N-H Stretching), 1551cm^{-1}(C-C aromatic stretching),1280 cm^{-1}(C-N Stretching due to aromatic amine),1376 cm^{-1}(C-H symmetric bending 841cm^{-1}(C-Cl Stretching) etc. There is no appearance of any new peak and absence of any interfering peak in the FTIR spectra of pure dug when compared to that of physical mixture of drug and polymers. It indicates that there is no drug excipient incompatibility.

3.4.6.2 DSC Analysis

DSC study provides the information about the physical characteristics of the samples. Any significant changes in the thermal characteristics of the drug and used excipients is demonstrated in the compatibility profile.[10] Thermograms of the pure drug of diclofenac potassium is shown in the Figure 6. A sharp melting point transition of diclofenac potassium pure drug was observed at 283.28°C, the onset of transition was started at 261.8°C. The thermogram of diclofenac potassium and AGP showed the endothermic peak at 318.45°C and the thermogram of Physical mixture of diclofenac potassium, AGP & HPMC showed the endothermic peak at 290.5°C, which was observed to be with lesser intensity peak value as compared to pure drug. This indicates that the the mixture of samples has not affected the nature of drug and there is no major physico-chemical changes in diclofenac potassium.

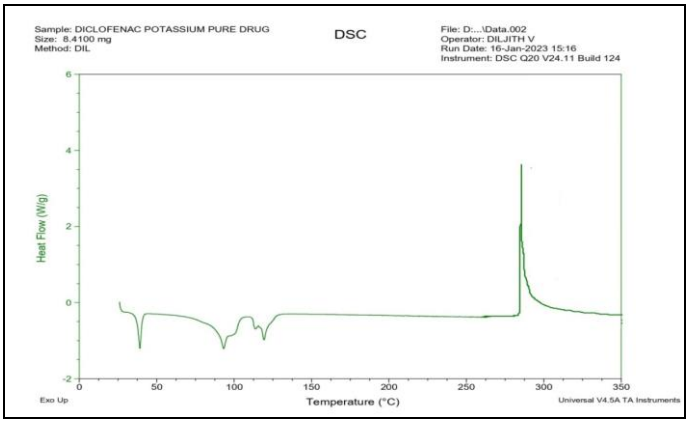

Fig. no. 6: DSC thermogram of diclofenac potassium pure drug.

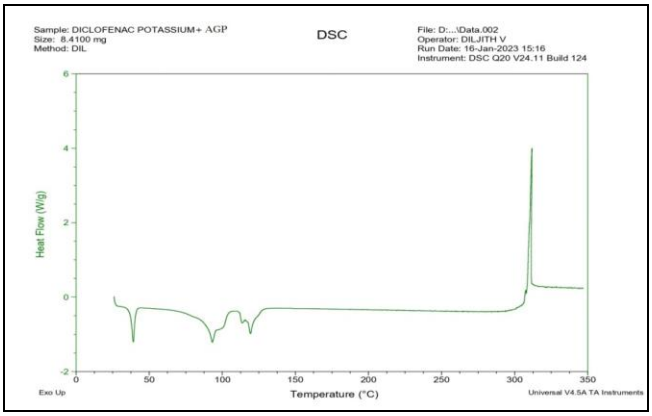

Fig. no. 7: DSC thermogram of diclofenac potassium pure drug + AGP.

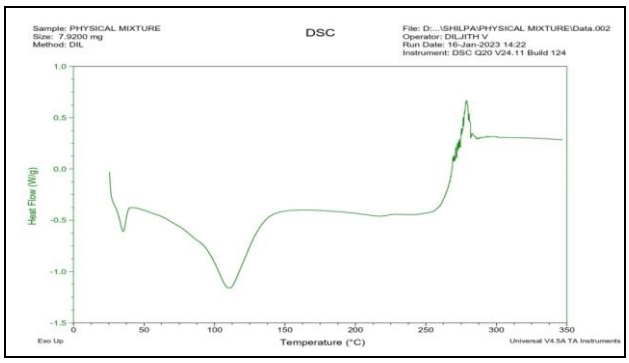

Fig. no. 8: DSC thermogram of Physical mixture (DFP+AGP+HPMC).

3.5 Precompression parameters of powder blend

Table 5: Precompression parameters of powder blend.

Formulation	Bulk density± SD (g/ml)	Tapped density± SD (g/ml)	Carr's index± SD (%)	Hausner's ratio± SD	Angle of repose ± SD (Θ)
F1	0.326 ± 0.014	0.369 ± 0.016	11.65 ±0.09	1.1319±0.0014	23.4°±0.574
F2	0.339 ± 0.015	0.39 ± 0.015	13.07 ±0.08	1.1504 ± 0.0012	24.5°±0.572
F3	0.326 ± 0.014	0.369 ± 0.016	11.65 ±0.09	1.1319 ± 0.0014	23.4°±0.574
F4	0.321 ± 0.013	0.36 ±0.014	10.83 ±0.07	1.1214 ± 0.0013	23.8°±0.573
F5	0.326 ± 0.015	0.369 ± 0.017	11.65 ±0.08	1.1319 ± 0.0015	25.1°±0.571
F6	0.324 ± 0.013	0.366 ± 0.015	11.47 ±0.07	1.1296 ± 0.0012	24.1°±0.571
F7	0.326 ± 0.014	0.369 ± 0.016	11.65 ±0.09	1.1319 ± 0.0014	23.4°±0.574
F8	0.357 ± 0.015	0.412 ± 0.015	13.34 ±0.08	1.1540 ± 0.0015	24.6°±0.573
F9	0.332 ± 0.013	0.379 ± 0.014	12.40 ±0.07	1.1415 ± 0.0013	23.9°±0.573
F10	0.326 ± 0.014	0.369 ± 0.016	11.65 ±0.09	1.1319 ± 0.0014	23.4°±0.574

F11	0.331 ± 0.015	0.379 ± 0.014	12.66 ±0.08	1.1450 ± 0.0015	23.9°±0.571
F12	0.326 ± 0.014	0.369 ± 0.016	11.65 ±0.09	1.1319 ± 0.0014	23.4°±0.574
F13	0.322 ± 0.013	0.361 ± 0.014	10.80 ±0.07	1.1211 ± 0.0013	23.1°±0.573

All values are expressed as mean ± SD, n=3

3.5.2 Bulk density and Tapped density

The bulk density and tapped density of the powder blend was in the range of 0.321 to 0.357 g/ml, 0.361 to 0.412 g/ml respectively and which indicates that the powder blend were not bulky and has good packaging characteristics.

3.5.3 Compressibility Index (CI)

Compressibility index were found in between 10.80 to 13.34%, which indicates that the powder blend have excellent flow property or compression.

3.5.4 Hausner's ratio

The Hausner's ratio of the powder blend was found to be in the range of 1.1211to 1.1540, which indicates good flow properties of powder blend.

3.5.5 Angle of repose (θ)

The angle of repose for the formulated powder blends were found to be in the range of 23.1 to 24.6 which indicates excellent flow properties of powder blend.

3.6 Post compression parameters of sustained release tablets

3.6.2 Physical properties of sustained release tablets

Table 6: Post compression parameters of sustained release tablet.

Formulation	Thickness ± SD (mm)	Hardness ± SD (Kg/cm^2)	Friability (%)	Drug content± SD (%)	Weight variation ± SD (%)
F1	3.55 ± 0.40	5.32 ± 0.37	0.33 ± 0.015	97.95 ± 0.21	1.55 ± 0.42
F2	3.62 ± 0.40	4.91 ± 0.42	0.37 ± 0.014	98.54 ± 0.42	1.49 ± 0.43
F3	3.55 ± 0.40	5.32 ± 0.37	0.34 ± 0.016	97.95 ± 0.21	1.54 ± 0.42
F4	3.65 ± 0.51	5.74 ± 0.35	0.26 ± 0.014	98.83 ± 0.34	1.32 ± 0.41
F5	3.45 ± 0.40	5.21 ± 0.42	0.35 ± 0.015	97.85 ± 0.41	1.56 ± 0.44
F6	3.25 ± 0.40	5.55 ± 0.34	0.29 ± 0.014	99.28 ± 0.33	1.45 ± 0.38
F7	3.55 ± 0.40	5.32 ± 0.37	0.33 ± 0.012	97.95 ± 0.21	1.56 ± 0.42
F8	3.41 ± 0.37	4.52 ± 0.40	0.39 ± 0.014	99.23 ±0.24	1.52 ± 0.42
F9	3.51 ± 0.42	5.11 ± 0.34	0.36 ± 0.015	97.23 ±0.19	1.49 ± 0.43
F10	3.55 ± 0.40	5.32 ± 0.37	0.34 ± 0.015	97.95 ± 0.21	1.5 5± 0.42
F11	3.42 ± 0.41	4.92 ± 0.42	0.38 ± 0.014	98.72 ± 0.43	1.46 ± 0.43
F12	3.55 ± 0.40	5.32 ± 0.37	0.34 ± 0.014	97.95 ± 0.21	1.54 ± 0.42
F13	3.62 ± 0.42	5.69 ± 0.40	0.28 ± 0.013	99.26 ± 0.51	1.36 ± 0.41

All values are expressed as mean ± SD, n=3

Tablets with different formulation codes were subjected to various evaluation tests, such as thickness, hardness, friability, and uniformity of drug content. The results of these parameters are given in Table 5. All the formulations showed uniform thickness of 3.41-3.65mm, uniform weight was observed with varying formulation code. In the weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250mg is ±5% difference.[11] The average percentage deviation of all the formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of the tablets (n = 10) ranged from 4.52 ± 0.40 to 5.74 ± 0.35 kg/cm^2. The percentage friability of the tablets (n = 10) ranged from 0.26 ± 0.014 to 0.38 ± 0.014. The percentage friability for all the tablet formulations were below 1%. Drug content was found to be uniform among different batches of the tablets (n =20) and ranged from 97.23 ±0.19 to 99.26 ± 0.51.Thus all the physical characteristics of drug was found to be within acceptable limits.

3.6.3 *In vitro* drug release studies

The *in vitro* drug release of all the 13 formulations were determined using USP apparatus I (Basket type) with 0.1N HCl as dissolution medium for first 2hrs and then phosphate buffer pH 6.8 for next 10hrs. Among all the formulations, F6 showed greater prolonged *in vitro* drug release (100%) than all other formulations at the end of 12 hrs. The F8 formulation which is prepared without any polymers showed almost complete drug release within 5hrs.Formulation F2 containing 70mg HPMC alone as retardant showed a complete release at the end of 9hrs.The formulations prepared with AGP alone (F9 & F11) disintegrated completely within 8th & 9th hours respectively. The formulations F1, F3, F4, F6, F7, F10, F12 & F13 prepared with combination of aloevera gel powder and HPMC showed best *in vitro* drug release characteristics and extended the release upto 12hrs than the formulation with a single polymer.

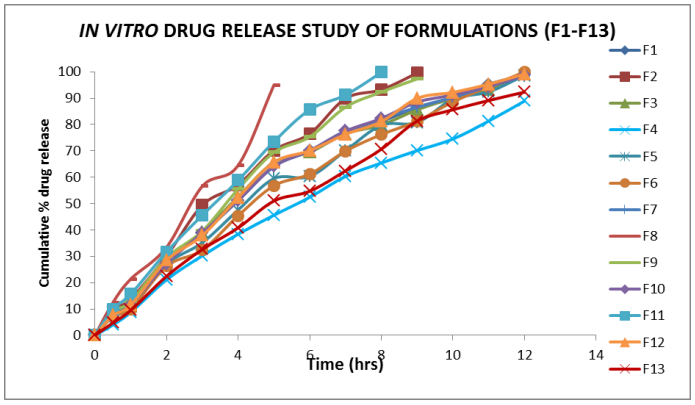

Fig. no. 9: In vitro drug release of formulations F1-F13.

3.7 Effect of polymer concentration on matrix integrity

The maintenance of the integrity of the matrix in the tablets is essential parameter in the controlled release formulations. If the tablets fail to maintain its physical integrity it may disintegrate rapidly. If the tablet disintegrates it may lead to damage of the matrix and subsequent drug release before the expected lag time. The tablet integrity was influenced by the polymers incorporated in the formulations.[10] AGP played a vital role in the maintaining the integrity of tablet matrix. Whereas HPMC also helped in maintaining the integrity by acting as a swelling agent in the preparation. AGP used in concentration between (40-80mg) was found to be suitable in maintaining the matrix of the tablets. MCC also improved the compression properties during the tablet preparation. From the dissolution profile it was found that formulation F8 (prepared without any polymers) showed complete release within 5hrs.The formulations F9 & F11 (prepared with AGP alone) dissolved completely within 8th & 9th hours respectively during the dissolution study. The formulation F2 (prepared only with HPMC) dissolved within 9 hours of the dissolution profile. Formulations F1,F3,F4,F6,F7,F10,F12, & F13 (prepared with both HPMC & AGP) extended the drug release up to 12hrs.So this indicated that to maintain the matrix AGP is essential. The tablets prepared with AGP in combination with HPMC demonstrated better performance rather than using alone.

3.8 Optimization by Design Expert Software

Central composite design was used to investigate the effect of the two independent variables and their potential interaction. The average values were submitted to multiple regression analysis using Design Expert software (Version 13.0.7.0, Stat- Ease). Polynomial models were generated for all the response variables.

Table no. 7: Formulations of Diclofenac potassium matrix tablets with the levels of independent Variables and Observed values for the response variable.

Formulations	Independent variables		Observed responses		
	X1 (mg)	X2 (mg)	Y1 (%)	Y2 (%)	Y3 (hrs)
F1	40	70	27.95	98.88	3.9
F2	0	70	30.1	96.3	3.5
F3	40	70	28.21	99.1	3.8
F4	80	140	21.1	88.9	5.2
F5	0	140	24.1	98.63	4.2
F6	80	70	26.21	100	4.4
F7	40	70	28.31	98.34	3.9
F8	0	0	33.42	95	3.1
F9	80	0	29.35	97.3	3.6
F10	40	70	27.23	98.65	3.9
F11	40	0	31.65	96.1	3.4
F12	40	70	28.45	99.2	3.8
F13	40	140	22.4	92.3	4.9

The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square.[1]

The fit of the model was evaluated using R^2-values. As observed from, (Table 8) R^2values was >0.95 for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2, value was in good agreement with the Adjusted R^2 value (the difference is less than 0.2), indicating the reliability of the models.

Table no. 8: Numerical test results of model adequacy checking for influence of independent variables on response variables.

Response	Source	Sequential P Value	Lack of fit Pvalue	R-squared	Adjusted R-squared	Predicted R-squared	Adequate precision	% CV
Y1	Quadratic	0.0055	0.899	0.9927	0.9874	0.9818	47.5284	1.41
Y2	Quadratic	0.0139	0.061	0.9681	0.9553	0.9502	38.1902	1.79
Y3	Quadratic	0.0270	0.072	0.9857	0.9755	0.9061	35.3091	2.31

Based on the fit summary quadratic model was selected as best fit for %Release at 2hrs, % release at 12hrs and $t_{50\%}$. The results of ANOVA (table 8) indicated that the selected models were significant($p < 0.05$) and the lack of fit (LOF) were not significant (p-values >0.05) for all the response variables indicating the reliability of the models.

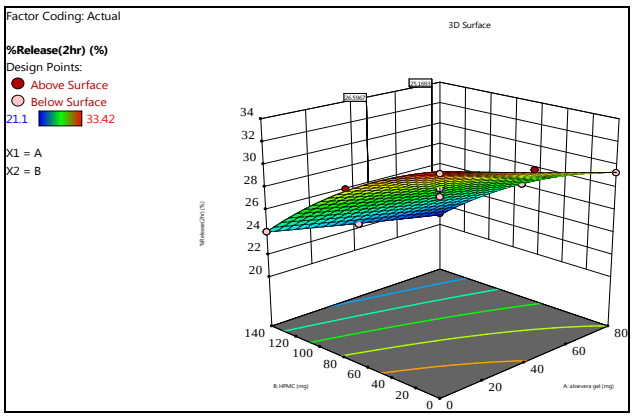

Fig. no. 10: 3-D response surface plots for effect of concentration of aloevera gel powder and HPMC on %release at 2hrs.

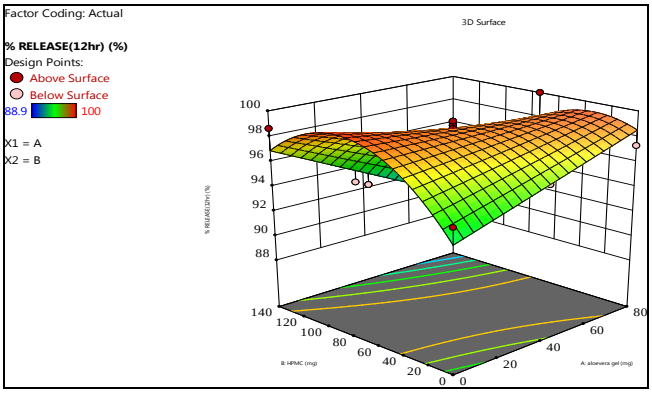

Fig. no. 11: 3-D response surface plots for effect of concentration of aloevera gel powder and HPMC on %release at 12hrs.

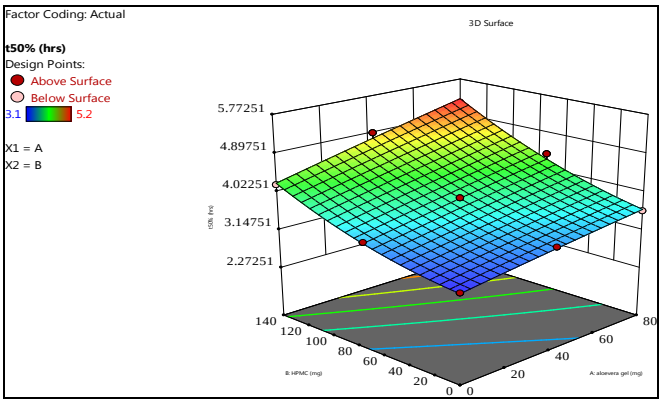

Fig. no. 12: 3-D response surface plots for effect of concentration of aloevera gel powder and HPMC on %release at 12hrs.

The desirability function approach is one of the most widely used methods for optimization of multiple responses. Overall desirability function is a measure of how well the combined goals for all responses are satisfied. Desirability function ranges from 0 to 1, with value closer to one indicating a higher satisfaction of response goal(s). The numerical optimization tool provided 6 sets of optimal solutions among which 80mg aloevera gel powder and 71.603mg of HPMC was selected (by the software) as optimized concentration with desirability of 1.0.

Table no. 9: Desirability table showing solutions suggested and its desirability.

Number	Aloevera gel powder	HPMC	% Release (2hr)	% Release (12hr)	$t_{50\%}$	Desirability	
1	80.000	71.063	26.210	97.957	4.288	1.000	Selected
2	80.000	71.628	26.176	97.920	4.295	0.991	
3	78.630	72.034	26.210	97.917	4.287	0.930	
4	74.990	74.573	26.210	97.818	4.283	0.925	
5	74.475	74.927	26.210	97.806	4.282	0.925	
6	43.869	94.199	26.210	97.510	4.197	0.892	

The area of optimized formulation was also ratified using overlay plot as shown in Fig 13 in which the yellow region represents the area satisfying the imposed criteria.

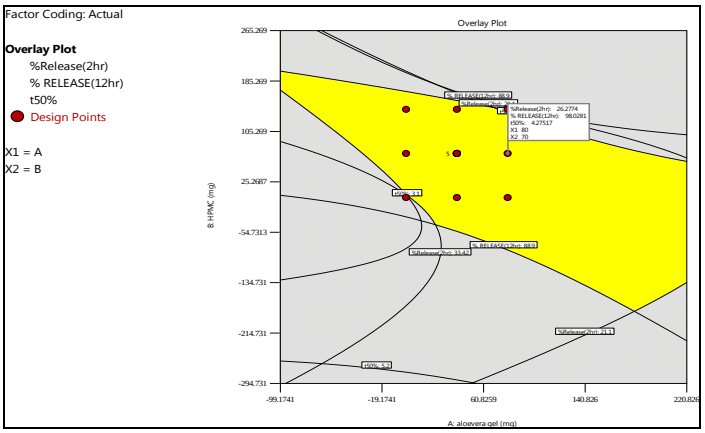

Fig. no. 13: Overlay plot of optimized formulation of diclofenac potassium matrix tablets.

Fig. no. 14: Photograph of optimized formulation.

To confirm the validity of obtained optimal formulation, experiments were carried out in triplicate at the optimal combinations of the factors (X1 = 80 mg, X2 = 71.063 mg). Table 10 provides the predicted values and experimental results for the response variables and the percentage error obtained at optimal levels. The observed values of response variables were close to the predicted values (error <5%), indicating the reliability of developed mathematical models.

Table 10: Response values of predicted, Experimental and Percentage error obtained at optimal levels of the factors.

Response	Predicted value	Experimental value	% Error
Y1 (%Release 2hrs)	26.21	26.09	-0.45
Y2 (%Release 12hrs)	97.9571	98.1	0.15
Y3($t_{50\%}$)	4.28843	4.12	-0.04

3.9 Kinetic studies

Release kinetics study on the optimized formulation revealed that First order model was the best fit model with R^2>0.990. For matrix tablets, an n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism.[12] The drug release mechanism from the optimized formulation was also evaluated using the Korsmeyer-Peppas model and the results showed that n value ranges from 0.45 to 0.89 indicating drug release from the optimized formulation follows anomalous non-Fickian diffusion release mechanism.

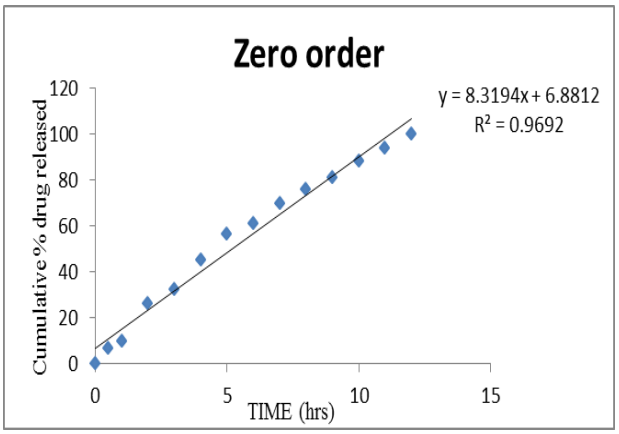

Fig. no. 15: Zero order release plot of optimized formulation.

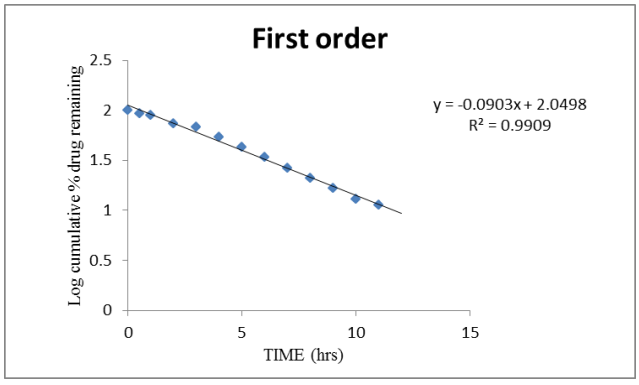

Fig. no. 16: First order release plot of optimized formulation.

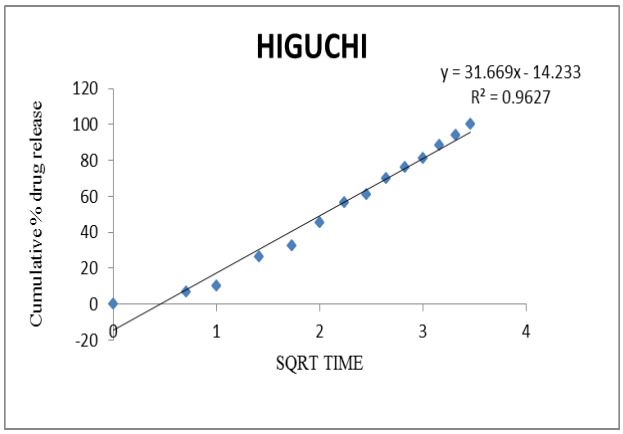

Fig. no. 17: Higuchi release plot of optimized formulation.

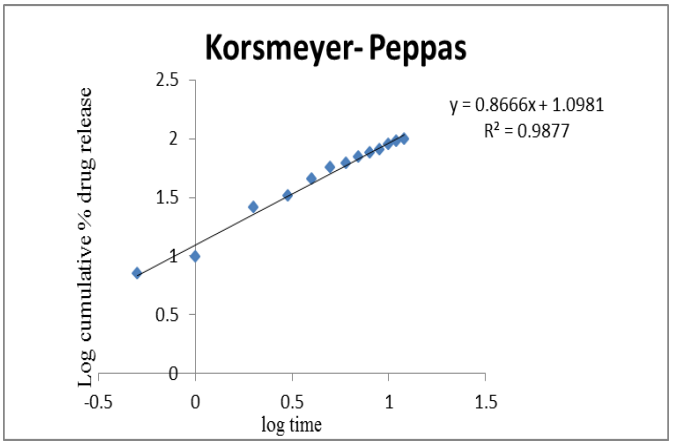

Fig. no. 18: Korsmeyer-Peppas release plot of optimized formulation.

Table 11: Drug release kinetics of optimized formulation.

Formulation	Zero order	First Order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
AGP-80mg HPMC-71.06mg	0.9692	0.9909	0.9627	0.9877	0.8666

3.10 Stability studies

The optimized formulation was subjected for stability studies as per ICH Guidelines for 3 months. It showed that the prepared floating tablets passed stability studies with not much significant changes in hardness, friability, drug content, and *in vitro* drug release(12hrs).

Table no. 12: Results of stability studies.

Storage condition	Sampling interval	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	In vitro drug release (12hrs) (%)
40ºC ± 2ºC at 75% ± 5%RH	Initial study	5.9 ± 0.40	0.26	99.56 ± 0.51	99.4
	30 days	5.9 ± 0.35	0.262	99.45 ± 0.59	99.2
	90 days	5.9 ± 0.16	0.266	99.26 ± 0.24	98.9
25ºC ± 2ºC at 60% ± 5% RH	Initial study	5.9 ± 0.40	0.26	99.56 ± 0.51	99.4
	30 days	5.9 ± 0.38	0.262	99.51 ± 0.23	99.3
	90 days	5.9 ± 0.26	0.264	98.49± 0.58	99.2
5ºC ± 3ºC	Initial study	5.9 ± 0.40	0.26	99.56 ± 0.51	99.4
	30 days	5.9 ± 0.31	0.265	99.54 ± 0.56	99.3
	90 days	5.9 ± 0.20	0.268	99.51 ± 0.58	99.3

4 CONCLUSION

The results of the micromeritic flow properties of gel powder is shown in Table 4, which indicates good flow property. Table 5 demonstrates the results of precompression studies of the final powder blend, where all the 13 formulations exhibited good flowability with optimal Hausner's ratio (<1.25) & angle of repose(<25). Table 6 displays the results of post compression studies of the formulated tablets. The average thickness of all the 13 formulations ranged from 3.41-3.65, they passed the test for hardness, friability, weight variation & had sufficient drug content. The dissolution profile (Fig 9) reveals that, F6 showed a complete drug release of 100% at the end of 12 hours. The numerical optimization tool provided 6 sets of optimal solutions among which 80mg aloevera gel powder and 71.603mg of HPMC was selected (by the software) as optimized concentration with desirability of 1.0 Results of kinetic study (Fig:15,16,17,18) implies that optimised formulation followed first order kinetics with non fickian release pattern. The results of stability studies (table no:12) as per ICH guidelines for 3 months indicates no significant changes in the properties of the optimized formulation, hence found to be stable. From the drug release profile it was observed that aloevera gel powder had a retardant effect. The study also proved that the amount of aloevera gel powder plays a vital role in improving various characteristics of dosage forms. Hence it can be concluded that aloevera gel powder is a potential and economical drug release retardant for the development of sustained release tablet dosage form.

5 ACKNOWLEDGEMENT

It gives me great pleasure to express my gratitude to the college management and guide Prof. Dr Suja C, Principal, Crescent College of Pharmaceutical Sciences, Payangadi, for providing the facilities for the successful completion of my project work.

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