Original Article

Development, In-Vitro And In-Vivo Evaluation Of Dexamethasone Sustained Release Matrix Tablets

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Abstract

The purpose of this study was to develop a sustained release matrix tablet that can effectively deliver dexamethasone for the treatment of Polycystic ovary syndrome (PCOS). Chitosan and HPMC K4M polymers were used to prepare matrix tablets by the direct compression method. The tablets were evaluated for various parameters such as thickness, friability, hardness, uniformity of weight, drug content, in-vitro dissolution and in-vivo studies. The study showed that the drug release can be modulated by varying the concentrations of polymers. The optimization studies indicated that the F7 formulation exhibited the best release profile of the drug and sustained the drug release for 8 hours with optimum mucoadhesive strength. The mechanism of drug release was investigated by fitting in vitro drug release data to several release kinetic models. The optimized F7 tablet floated continuously in the stomach area of rabbits for over 12 hr, so the gastric retention time could be extended to over 12 hr. The X-ray imaging of the tablet at the 6th hr and 12th hr indicated clearly that the tablet was present in the region of the stomach but had shifted its location in the abdomen. Overall, the study concluded that matrix tablets can be used as a successful carrier for the sustained delivery of dexamethasone with prolonged gastric residence time.

Keywords: Dexamethasone, Matrix tablets, sustained release, Chitosan and HPMC K4M, Gastric retention.

INTRODUCTION

Most oral drug products are designed to release the active drug immediately after oral administration. However, modified-release drug products have become increasingly common in recent years. These products are designed to control the rate and/or timing of drug release to achieve therapeutic or convenience objectives that cannot be achieved with conventional dosage forms. Modified-release dosage forms may be designed to release the drug slowly over an extended period, target specific areas of the body, or provide a constant release of the drug. These products can provide numerous benefits, including improved patient compliance, reduced side effects, and increased efficacy. These systems can provide a therapeutic amount of drug at the site of absorption and maintain the desired drug concentration, thereby reducing the potential for underdosing or overdosing [1-2].

Polymers are commonly used as a tool to control drug release from formulations in modified-release drug delivery systems. Polymers can provide unique properties that have not been achieved by other materials, such as controlled release properties, biocompatibility, and stability [3]. Therefore, polymers have extensive applications in drug delivery systems. However, it is important to note that other materials, such as lipids and metals, may also be used to control drug release from formulations [4].

Dexamethasone is a medication that is commonly used to treat chronic diseases like Polycystic ovary syndrome. The half-life of dexamethasone is approximately 4 to 5 hours, which means that single daily doses are often required to maintain adequate plasma concentrations [5-6]. By controlling the release of

dexamethasone in a formulation, it is possible to achieve a sustained release of the drug over a period of 20-24 hours at a predetermined rate. Optimization techniques, such as design of experiments (DOE), can be used to study the influence of formulation variables on the release profile of the drug. These techniques can help identify the optimal combination of formulation variables to achieve the desired release profile [7].

Design of experiments is a statistical approach that provides an effective means for studying the effect of various parameters on dependent variables, such as drug release. By varying different formulation variables, such as the type and concentration of polymers used in the formulation, it is possible to identify the optimal formulation that provides the desired release profile for dexamethasone [8-9].

the objective of this research work is to develop an optimized drug delivery system for the treatment of PCOS using dexamethasone as the active ingredient. By identifying the optimal combination of polymers and evaluating the drug release profile both in vitro and in vivo, the researchers hope to develop a formulation that can effectively treat PCOS with improved patient compliance and reduced potential for adverse effects.

MATERIALS

Dexamethasone was kindly gifted by Symbiotec Pharmalab Private Limited, Indore, Chitosan was purchased from Loba Chemie, Mumbai. HPMC K4M, Micro crystalline cellulose, PVP K30 were procured from Loba chemie, Mumbai. All other reagents and solvents were of analytical grade.

METHODS

Determination of wavelength maxima (λ_{max}) and Preparation of Calibration Curve by UV Analytical Method

The drug powder containing 10 mg of Dexamethasone is dissolved in 10 ml of methanol, and the volume is adjusted to 100 ml with 0.1N HCl. Dilutions are made to obtain a range of concentrations from 5 to 50 µg/ml. A solution with a concentration of 10 µg/ml is scanned in a UV spectrophotometer to determine the maximum absorbance of the solution, which is found to be 244 nm. A calibration graph is plotted with concentration on the X-axis and absorbance on the Y-axis, following Beer's law. The regression value is determined from the calibration curve [10].

FTIR of Dexamethasone

FTIR is used to identify the functional groups in the molecule. IR transmission spectra were obtained by using FTIR spectrophotometer by KBr pellets method. Small quantity of drug was used for IR analysis. The scanning range was 400–4000 cm^{-1}; various peaks in infrared spectrum were interpreted for different group [11].

Drug-Excipients Compatibility Studies [12]

Drug-Excipient compatibility was carried out by FTIR analysis. IR spectrums of pure drug (Dexamethasone) and mixture of drug with polymer (Chitosan, HPMC K4M and PVP K30) was obtained. The IR absorption spectra of the pure drug and physical admixtures of drug with various excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method and observed for characteristic peaks of drug. The obtained spectra of physical admixtures was observed for major peaks and recorded.

Precompression Characterization

The flow properties of drug blend with the excipients were determined in terms of angle of repose, Car's index, and Hausners ratio. The bulk density and tapped density were determined, and from this data Car's index, and Hausners ratio were calculated [13-14].

Formulation of Matrix Tablets of Dexamethasone

Different batches of matrix tablets containing 20 mg of dexamethasone were prepared using direct compression method. All the necessary components given in table 1 were previously sieved through a mesh size of 16 mm and mixed homogeneously. Talc and

magnesium stearate were finally added as glidant and lubricants. The tablets were compressed using rotary compression machine. The total weight of tablet was 100mg
and each tablet contains 20 mg of dexamethasone [15].

Table 1 Formulation composition of matrix tablets of Dexamethasone

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dexamethasone	20	20	20	20	20	20	20	20	20
Chitosan	150	50	150	100	50	150	50	100	100
HPMC K4 M	150	50	50	150	150	100	100	100	50
Microcrystalline cellulose	60	260	160	110	160	110	210	160	210
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

Evaluation of prepared Matrix Tablets [16-19]

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed, in grams on an analytical balance. Results are expressed as mean values ± SD.

Tablet thickness

A Vernier calipers was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values ± SD.

Drug content uniformity

Ten tablets were individually weighed, crushed and quantity of powder equivalent to the mass of one tablet was extracted in 100 ml of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm). The drug content was determined by UV spectroscopy at a wavelength 244 nm after a suitable dilution with 0.1N HCl [17-18].

Tablet Friability

According to the BP specifications 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, de-dusted and accurately weighed. The percent weight loss was calculated.

Drug release studies

Drug release studies of the prepared extended release gastroretentive tablets were performed in triplicate, in a USP Dissolution Apparatus, type II (Paddle method) at 37±0.5°C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 ml of 0.1N HCl solution (pH 1.2). Aliquots of 5ml were withdrawn from the dissolution apparatus at different time intervals & filtered through a cellulose acetate membrane (0.45µm). The drug content was determined spectrophotometrically at a wavelength of 244nm. At each time of withdrawal, 5ml of fresh medium was replaced into dissolution flask.

Measurement of Mucoadhesive Strength

Mucoadhesive strength was evaluated using a texture analyzer (CEB Texture Analyzer). Fresh goatgastric mucosa was obtained from a local slaughter house and was used within 2 h of slaughtering. The mucosal membrane was washed with distilled water and then with 0.1N HCl subsequently it was fixed in between two plates and placed it in beaker. The tablet carefully attached to a 10-mm cylindrical probe by a bioadhesive tape. The probe attached with tablet was moved downward toward mucosa at a constant speed of 1mm/s until a predetermined compressive force of 0.5 N with holding time 60 s and load cell 1000gm. The probe was then removed with return speed of 1 mm/s to a distance of 15 mm and maximum detachment weight was determined for each sample. For each new sample, a different mucosa sample was used [20].

In vivo Pharmacokinetic studies

The pharmacokinetic studies of prepared tablets were carried out in Albino Rabbits weighing 2-2.5 Kg and the protocol was approved by Institutional Animal Ethical Committee (IAEC) of Adina Institute of Pharmaceutical sciences sagar, with Registration no. 1546/POE/S/11/CPCSEA. All animal were maintained, treated, housed and performed in accordance with the guideline of IAEC.

In vivo study was carried out making two groups of healthy Albino rabbits. Each group consists of six rabbits (n=6). Group I was kept as positive control (pure drug tablet, marketed.) while Group II animals were given prepared optimized matrix tablets. All rabbits were fasted overnight. To Group I, Pure dexamethasone drug and to Group II, dexamethasone matrix tablet formulation - were administered by oral route by gastric intubation method. Tablet was ingested with 20 ml of water using Latex Catheter (Size 14 French, 16 inch long). Rabbits were placed in metalic cages and blood samples were collected by using 27 gauge needle from the marginal ear vein into heparinized tubes at time intervals of 0.5, 1, 2, 4, 6, 12, 24 hours. Xylene was applied to the shaved marginal ear vein, which causes blood vessel to dilate. The samples were subjected to centrifugation by adding 50µl of Acetonitrile cyclomix at 8000 rpm for 20 mins and the supernatant was collected by using micropipette. After filtration 20µl sample was injected into the HPLC system [21-22].

In vivo floating behavior

The in vivo buoyancy of the matrix tablet was evaluated by preparing barium sulphate loaded tablets uing the same procedure for the preparation of floating matrix tablets except for using 10 mg barium sulphate (BaSO4) instead of the drug. The radiographic studies were conducted in young and healthy male albino rabbits. In order to standardize the conditions of gastrointestinal motility, the animals were fasted for 12 hours prior to the commencement of the experiment and the first radiographic image of the animal subject was taken to ensure the absence of any radiopaque material in the gastrointestinal tract. The rabbits were made to swallow barium sulphate loaded matrix tablets with 20 ml of water.

For radiographic imaging, the rabbits were placed on the image board and location of the formulation in the stomach was monitored by keeping the subjects in front of X-ray machine (WiproGEDX-300, SAIMS, Indore, India). Gastric radiography was conducted at the intervals of 0 hour, 2 hr, 6 hr and 12 hr [21-22].

RESULTS AND DISCUSSION

Determination of wavelength maxima (λ_{max}) and Calibration Curve of drug

UV spectra of drug was obtained by scanning drug solutions (10µg/ml) showed maximum absorption at 244 nm. Reported λmax of drug is 244 nm. So it can be concluded that the given drug was Dexamethasone. Calibration curve was prepared in 0.1N HCl at 244nm and linearly regressed. The correlation coefficient for standard curves was found to be very near to one which indicates good co-linear correlation between concentration 5-50 µg/ml (Fig. 2). Hence, drugs are following Beer Lambert Law in the above range.

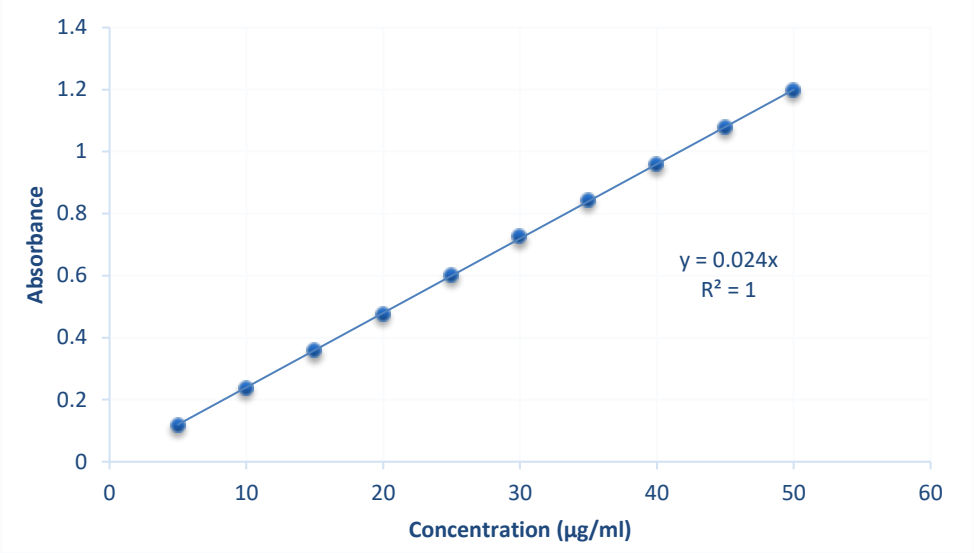

Fig. 1: Calibration curve of Dexamethasone in 0.1N HCl at 244nm

FTIR spectroscopy of drug

FTIR spectra of Dexamethasone was obtained and compared with reference IR spectra for identification and confirmation of various functional groups. Interpretation of FTIR spectra of Dexamethasone suggests that the observed peak list meets with that of the reference peak list. The observation confirms that the drug obtained is pure.

Drug-Excipients compatibility study

FTIR analysis was performed in order to confirm the drug and excipients interaction. The scan was examined for the existence of major drug peaks, the shifting and masking of drug peaks, and the formation of new drug peaks as a result of excipient interaction. There are no extra peaks seen other than the normal peak in the spectra of the mixture of the drug and excipients and so there is no interaction with the drug and excipient and they are compatible with each other.

Precompression characterization

The bulk density of all formulations ranges from 0.36g/cm^3 to 0.45g/cm^3. The tapped density of all the formulations ranges from 0.45g/cm^3 to 0.56g/cm^3. The angle of repose of all formulations was found in a range of 25˚.5' to 29˚.6'. The compressibility index of all the formulations ranges from 8.69 to 30.35. The Hausner's ratio for powder blends of all formulations ranges from 1.09 to 1.43. It was observed from the results that the powder blends of all formulations have good flow properties except for formulations (F1, F2 and F7) (Table 2).

Table 2 Pre-compression characterization of drug and excipients blend

Formula Code	PARAMETERS				
	Angle of Repose (θ)	BD (g/ml)	TD (g/ml)	CI (%)	HR
F-1	28.2	0.36	0.49	26.53	1.36
F-2	25.5	0.39	0.56	30.35	1.43
F-3	28.1	0.39	0.48	18.75	1.23
F-4	29.6	0.42	0.46	8.69	1.09
F-5	25.7	0.40	0.46	13.04	1.15
F-6	27.2	0.38	0.45	15.55	1.18

F-7	27.1	0.41	0.53	22.64	1.29
F-8	27.8	0.39	0.46	15.21	1.17
F-9	27.4	0.45	0.54	16.66	1.20

Formulation of Mucoadhesive Matrix Tablets:

Optimization Study

The design of experiment (DOE) is an approach in which process variables are first screened and then optimized to determine best settings for the variables. The full factorial design is a quadratic design that requires 3 levels (-1, 0, +1) for each factor. The concentration of Chitosan and HPMC K4M was selected as the independent variables, whereas Drug release and mucoadhesive strength were selected as the dependent variables. The interactions between the factors were demonstrated using 3-D graphs. The experimental values obtained were compared with those predicted by the mathematical models. The data generated is given in Table 4, which was analyzed using Design Expert software version 11.0, and polynomial equations were obtained for the same.

Table 4: 3^2 Experimental designs with response

S. no.	Concentration of Chitosan (mg)	Concentration of HPMC K4M (mg)	In-vitro drug release (%)	Mucoadhesive strength (gm)
F1.	150	150	64.26	78.93
F2.	50	50	65.82	57.48
F3.	150	50	87.24	80.12
F4.	100	150	66.51	64.38
F5.	50	150	60.20	56.64
F6.	150	100	79.84	74.52
F7.	50	100	71.56	59.87
F8.	100	100	81.12	68.08
F9.	100	50	89.58	72.44

The optimized batch was obtained from statistical analysis of response plots using design expert software version 11. In the software, the criterion was selected in the range for % drug release and mucoadhesive strength; the desirability was found to be 1.000. The desirability concentration of Chitosan 150 (mg) and HPMC K4 M was found to be 50 (mg).

Evaluation of prepared Matrix Tablets

The hardness for tablets of all the formulations was found to be in range of 7.65±0.58 kg/cm^2 to 8.05±0.50kg/cm^2. The results indicate that the friability for tablets of all formulations was below 1%and hence passes the test. The weight variation for tablets of all formulations was found to be within the range of 5%. The results indicate that all tablets of each formulation were of uniform weight. The thickness for tablets of all formulations was found to be 4.39 to 4.48 mm. The drug contents for tablets of all the formulations ranges from 95.20% to 98.84%. The drug content was analyzed at 244nm (Table 4).

Table 4: Post-compression evaluation of matrix tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9

Hardness ($Kg/cm^{2)}$	7.8	7.7	7.7	8.1	7.9	7.6	7.8	7.9	7.8
% Weight variation	3.2	3.2	1.8	3.6	2.5	2.8	1.8	2.4	2.5
Thickness (mm)	4.42	4.41	4.42	4.48	4.39	4.42	4.44	4.43	4.46
Friability (%)	0.68	0.66	0.62	0.67	0.66	0.62	0.68	0.65	0.63
% Drug Content	95.20	98.84	98.84	98.15	98.02	98.26	97.58	98.18	98.67

In vitro drug release of tablets

The concentration of polymer in the sustained release layer was a key factor in controlling the drug release. The release rate of all formulations was found to be polymer concentration dependant. Increased polymer concentration reduced the diffusion of the drug from the matrix. If the viscosity increases, the entrapment of the drug is tightly bound in between the cross-links of the polymer; the drug will take time to release from the patches. From the results, it can be concluded that there was an increase in the duration of drug release with an increase in polymer concentration in the formula (Fig 2).

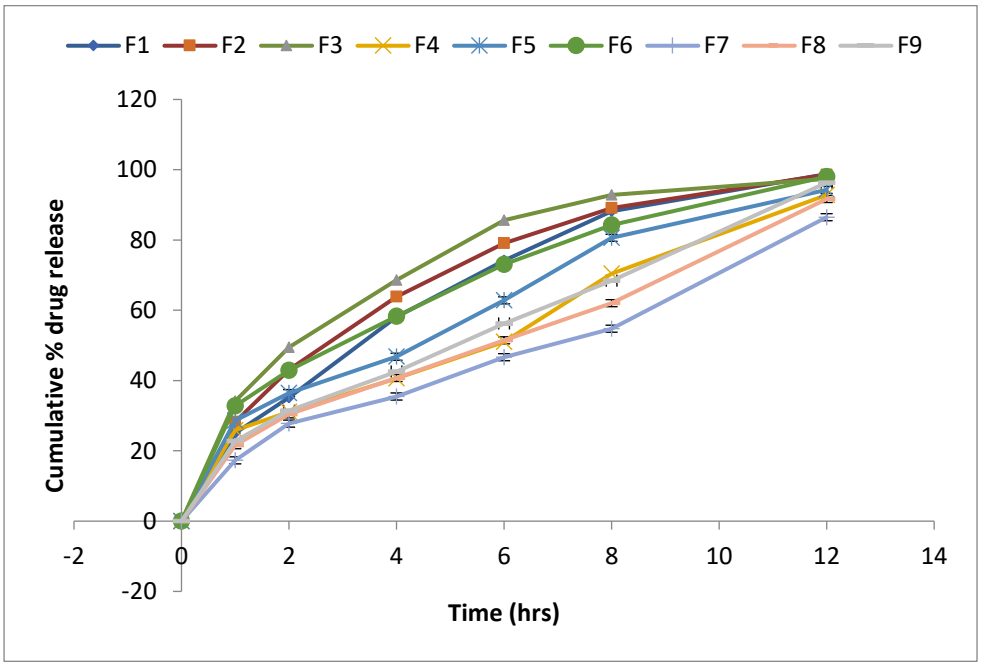

Fig. 2. Comparative drug release from formulations F1-F9

Measurement of Mucoadhesive Strength

The mucoadhesive strength for F1 to F9 batches was determined using the mucosal surface adhesion model. Bioadhesive force values ranged from 56.02 gm to 80gm. One of the key physical features of mucoadhesive tablets determined by the aforementioned method is the in-vitro retention time. Retention time values ranged from 3.5 h to 8.5 h. The result showed that, as the concentration of mucoadhesive polymer increased, the retention time also increased (Fig 3).

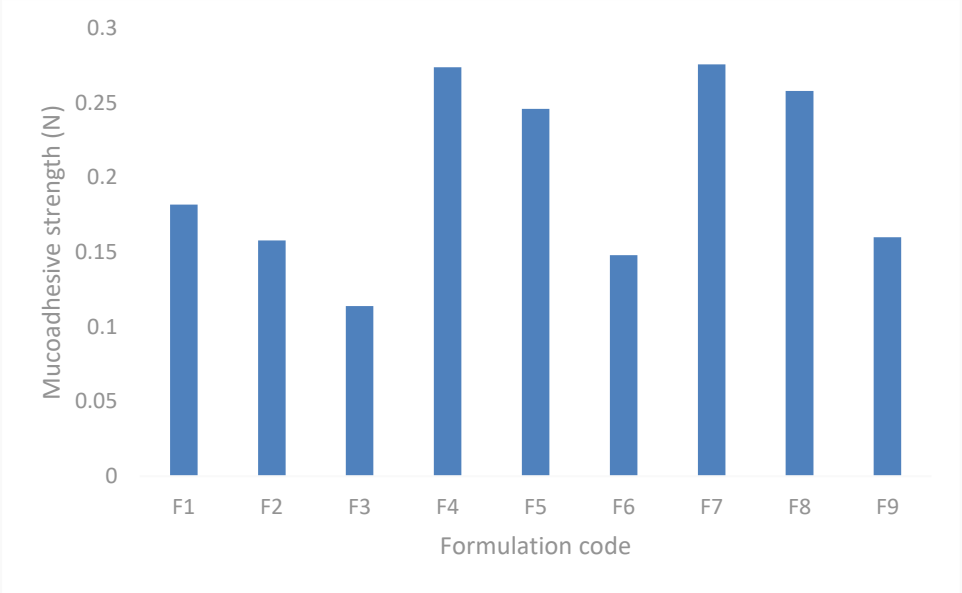

Fig. 3 Mucoadhesive strength for F1 to F9 batches

In vivo Pharmacokinetic Parameters Evaluation

These parameters are compulsory for determination of bioavailability, such as maximum concentration of serum (Cmax), time to reach the maximum conc. of serum (Tmax), area obtained under the plasma-concentration time curve(AUC), Volume of distribution(Vd), half-life ($t_{1/2}$), mean residence time (MRT) and clearance(Cl_T). Table 5 depicts plasma concentration values and bioavailability parameters of reference marketed formulation and prepared controlled release formulation F7.

Table 5. Pharmacokinetic parameters of optimized Controlled release tablet (F7)

Sub	T_{max} (h)	C_{max} (µg/mL)	t1/2(h)	MRT	Cl	Vd (mL)	AUC_{0-t}	AUC extrapolate	$AUC_{0-\infty}$	Total AUMC	K_{el}
1	12	0.8	5.32	0.085	180.2	6092.6	382.26	2.604	384.96	3694.7	6.645
2	12	0.82	6.27	0.086	160.4	5980.4	398.17	15.19	413.36	5222.4	8.752
3	12	0.83	5.84	0.081	130.3	5988.2	481.82	19.28	501.1	7876.8	10.942
4	12	0.81	4.87	0.078	140.2	6002.1	373.28	1.269	374.94	4361.5	7.955
5	12	0.79	5.06	0.076	145.2	5998.2	363.14	1.93	365.07	3712.5	7.041
6	12	0.85	5.42	0.086	150.2	6010.2	389.12	1.21	399.34	4213	7.201

In vivo floating behavior

The X-ray image clearly illustrated the absence of the tablet in the rabbit's GIT. Two hours after the oral administration of the tablet, an X-ray image of the stomach was taken and the F7 formulation was clearly detected in the stomach's upper portion. The X-ray imaging of the tablet at the 6th hr and 12th hr indicated clearly that the tablet was present in the region of the stomach but had shifted its location in the stomach area. This demonstrated its gastric retention. This experiment revealed that the optimized F7 floated continuously in the stomach area of the rabbits, so the gastric retention time could be extended to over 12 hr.

CONCLUSIONS

According to this study, the polymers HPMC K4M can create a regulated drug release pattern in the dexamethasone matrix tablets that have been prepared. Due to this formulation's strong mucoadhesive strength, it is likely to spend more time in the GIT, raising the bioavailability level. The study suggests that controlled release mucoadhesive matrix tablets of dexamethasone could be a promising alternative to traditional delivery methods for treating PCOS. The tablets were able to sustain drug release for up to 12 hours and showed enhanced bioavailability. However, further studies are needed to fully evaluate the therapeutic potential of these tablets before they can be used commercially.

DISCLOSURE

The authors report no conflicts of interest in this work.

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