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Original Article

APPLICATION OF NOVEL NATURAL POLYMER FOR CONTROLLING THE RELEASE OF FENOVERINE FROM CONTROLLED RELEASE MATRIX TABLETS

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Abstract

Objective: To explore a novel natural polymer, pullulan for controlling the release of fenoverine from matrix tablets and to elucidate the release kinetics of fenoverine from pullulan and HPMC matrices.

Methods: In this study we formulated monolithic matrix tablets containing of fenoverine as controlled-release tablets by direct compression using pullulan, HPMC (Hydroxypropyl methyl cellulose) K4M and HPMC K100M polymers and evaluated for hardness, thickness, friability, weight variation drug content, *in vitro* drug release characteristics and FTIR (Fourier transform infrared spectroscopy) and DSC (Differential scanning calorimetry) study.

Results: All the formulations showed compliance with pharmacopoeial standards. FTIR and DSC study indicated the absence of interaction between fenoverine and excipients. The formulation was optimized on the basis of acceptable tablet properties and *in vitro* drug release. The results of dissolution studies indicated that the formulation F5 [drug to polymer 1: 0.35] exhibited highest % cumulative drug release of 96.82±0.75 % at the end of 12 h. Optimised batch F5 showed super case II transport mechanism and followed zero order release kinetics. Short-term stability studies of the optimized formulation indicated that there were no significant changes observed in hardness, drug content and *in vitro* dissolution studies at the end of three months period. Similarity factor *f2* was found to be 89, which indicated similar dissolution profiles before and after stability study.

Conclusion: Based on above results we conclude that pullulan can be used as a polymer for retarding the release of drug from matrix formulations.

Keywords: Pullulan, Fenoverine, Hydroxypropyl methyl cellulose, Controlled release, *In vitro*

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INTRODUCTION

Controlled release systems include any drug delivery system that achieves slow release of drug over an extended period of time. Possible benefits of a properly designed controlled release dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profile attainable, increased convenience and patient compliance [1, 2]. In recent years oral, controlled drug delivery systems have gained increased importance and interest since it is necessary to improve the systemic absorption of the drugs and patient compliance. In addition, controlled drug delivery systems maintain uniform drug levels, reduce the dose, side effects, and increase the safety margin. There are several types of controlled release systems that are designed and categorized according to the mechanism they employ. These include diffusion controlled, dissolution controlled, erosion controlled, ion exchange controlled and transport controlled also known as osmotic pump system [3, 4, 30]. Matrix controlled release tablet formulations are the most fashionable and straightforward to formulate on a commercial scale. Matrix tablets serves as an important tool for oral controlled-release dosage forms. Hence, problems of conventional dosage forms, like patient non-compliance, local side effects, frequent administration and fluctuations in blood concentration levels were solved. Oral controlled release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency [1]. Matrix tablets may be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers [5]. The drug release in matrix drug delivery systems occur by both dissolution-controlled as well as diffusion controlled mechanisms [6-8]. The present work was intended to explore the natural polymer obtained from *Aureobasidium Pullulan* [9, 10, 26-29]. This natural polymer is extremely hydrophilic in nature. This polymer has been used for film forming ability by other researchers, novelty of study is its use as release retarding agent has not been explored. Fenoverine is chemically 10[4-piperonyl [1-piperazinyl] acetyl] phenothiazine with molecular formula $C_{26}H_{25}N_3O_3S$ [11, 12]. Fenoverine is an antispasmodic drug. It is used to relieve muscle spasm, used for disorders of the colon [Irritable bowel syndrome], abdominal pain, etc. [13, 14]. Fenoverine acts by modulating the gradient of calcium ions through the cell membrane. Fenoverine due to its poor aqueous solubility and poor wettabilty, less protein binding and its short biological half-life [5 to7 h] and therapeutic use in chronic conditions necessitates its formulation into controlled release dosage form [15, 16]. The objective of this investigation was to explore pullulan for its drug release controlling characteristics from controlled release dosage form.

MATERIALS AND METHODS

Materials

Fenoverine was a gift from Euro drug Laboratories, Hyderabad, India. HPMC K4M was procured from SD Laboratories, Mumbai, India, HPMC K100M from Research Lab., Fine Chemicals, Mumbai, India. Pullulan was procured from Gangaval chemicals, Mumbai, Spray dried lactose was obtained from Okasa Pharma, Satara, India. Talc and magnesium stearate were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. All other ingredients used throughout the study were of analytical grade and were used as received.

Methods

FTIR spectrum of fenoverine

The IR spectrum of fenoverine was recorded using Fourier transform infrared spectroscopy [ATR-FTIR] to check its purity. The spectrum was recorded over the wave number of 4000 to 400 cm^{-1}[19, 20].

Differential scanning calorimetry [DSC] of Fenoverine

DSC study was carried by using Mettler-Toledo DSC 821^e instrument [Switzerland]. About 2 mg of the fenoverine was sealed in the aluminum pan and heated at the rate of 10 °C/min, covering a

temperature range of 30 °C to 200 °C under a nitrogen atmosphere, at flow rate of 40 ml/min [21].

Drug–polymer compatibility study

FTIR study

FTIR spectra of HPMC K4M, HPMC K100M, pullulan and physical mixtures of fenoverine with polymer were recorded to study the interaction between them. The spectra were recorded over the wave number of 4000 to 400 cm^{-1}[19, 20].

DSC study

In order to assess the compatibility of fenoverine with a polymer, thermogram of pure fenoverine, HPMC K4M, HPMC K100M, pullulan polymers and formulations were recorded using Mettler-Toledo DSC 821^e instrument [Switzerland]. About 5 mg of the physical mixture was sealed in the aluminium pan and heated at the rate of 10 °C/min, covering a temperature range of 30 °C to 200 °C under a nitrogen atmosphere, at a flow rate of 40 ml/min [21, 25].

Formulation of controlled release tablets

Controlled release matrix tablets of fenoverine were prepared by using different concentrations of pullulan, HPMC K4M and HPMC K100M table 1. The entire excipients without talc were blended uniformly. After sufficient mixing of drug with other excipients, talc was added and further mixed for 5 min. The prepared powder mass was compressed with 11 mm punch on multi tooling compression machine [Rimek II Karnavati Eng. Ltd. Ahmedabad] to give a tablet of 500 mg weight.

Table 1: Formula for controlled release tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
Fenoveine	300	300	300	300	300	300	300
HPMC K4M	120	150	-	-	-	-	-
HPMC K100M	-	-	120	150	-	-	-
Pullulan	-	-	-	-	120	150	180
Spray dried lactose	60	30	60	30	60	30	-
Talc	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10
Total	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Note: All quantities are given in mg

Evaluation of tablets

Hardness and thickness

The hardness [kg/cm^2] of the prepared formulations was determined by using a Monsanto hardness tester and thickness was measured by micrometre screw gauge [mm] [n = 3] [22].

Friability

Friability of the prepared formulations was determined by using Roche friabilator [Campbell Electronics, Mumbai, India] [n = 20]. The tablet samples corresponding to 6.5 g were weighed accurately, placed in the drum. Drum was rotated 100 times, and then tablets were removed. Any loose dust from the tablets was removed, and accurate weight was taken, and the % friability was calculated from the weight of tablets before and after test [22].

Weight variation test

The weight of the tablet is measured to ensure that a tablet contains the specific and accurate amount of drug and excipients. Twenty tablets were selected randomly and weighed. The average weight of the tablet was determined. Not more than the two of the individual weights deviate from the average weight by more than 5 % and none deviates by more than 10% [n = 20] [22].

Drug content uniformity

Ten tablets were weighed and finely powdered, and powder equivalent to 300 mg of drug was accurately weighed and dissolved in 0.1 N HCl [pH 1.2 buffer]. The resulting solution was suitably diluted with 0.1N HCl [pH 1.2 buffer] and analyzed by Shimadzu UV spectrophotometer at 230 nm [13, 22, 31].

***In vitro* drug release study**

The USP type II rotating paddle method was used to study the drug release from the controlled release tablet. The dissolution medium used was 900 ml 0.1 N HCl [buffer pH 1.2]. The release study was performed at 37±0.5 °C, with a rotation speed at 100 rpm. Sample volumes of 0.5 ml were withdrawn at predetermined time intervals and filtered through 0.2 µm Whatman filter paper and analyzed after appropriate dilution by Double beam UV spectrophotometer at 230 nm. Sink conditions were maintained throughout the study. The study was carried out in triplicate [13].

Kinetics of *in vitro* drug release

To study the release kinetics of *in vitro* drug release, data was treated with different kinetic equations such as Zero order (equation 1), First order (equation 2), Hixon-Crowel (equation 3), Higuchi (equation 4) and Korsmeyer-Peppas (equation 5).

Zero order kinetics

$$W = k_1 t \quad \text{..... (1)}$$

First order Kinetics

$$\ln[100 - W] = \ln 100 - kt \quad \text{..... (2)}$$

Hixon-Crowell's Cube-Root Equation [Erosion Model]

$$[[10]^\circ - W]^{1/3} = 100^{1/3} - k_3 t \quad \text{..... (3)}$$

Higuchi's Square Root of Time Equation [Diffusion Model]

$$W = k_4 t^{1/2} \quad \text{..... (4)}$$

Korsmeyer peppers Equation [Diffusion/Relation Model]

$$M_t/M = k_5 t^n \quad \text{..... (5)}$$

Where, W is % drug release at time t and K_1–K_4 are release rate constants, depending on the kinetic model used. Mt/M is the fractional drug release into the dissolution medium and K_5 is a constant incorporating the structural and geometric characteristics of the tablet. The term n is the diffusional constant that characterizes the drug release transport mechanism. When n = 0.5, then the drug release mechanism is Fickian diffusion. If n<0.5 the mechanism is quasi-Fickian diffusion, and 0.5<n<1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion or zero order release kinetics could be observed [23, 24].

Stability studies

Optimised formulation was sealed in aluminium packaging coated internally with polyethene, and kept instability chamber maintained at a temperature of 45 °C±2 °C and relative humidity 75%±5% for 3 mo. Samples were withdrawn at 0, 30, 60 and 90 d and evaluated for the hardness, drug content and *in vitro* dissolution test [32].

RESULTS AND DISCUSSION

FTIR study

The IR spectrum of drug exhibited distinctive peaks at 1038.46 [cm^{-1}] due to C-N stretch [aliphatic amines] and peaks at 1234.24 [cm^{-1}] due to C-N stretch [aromatic amines]. The peaks at 1670.07 [cm^{-1}] due to C=O stretching, peak at 2808.73[cm^{-1}] due to C-H stretching, at 2964.65[cm^{-1}] due to C=C-H stretching and at 2931.26 [cm^{-1}] due to C-C-H stretching fig. 1.

DSC study

The DSC thermogram of the drug depicted a peak at 141.29 °C corresponding to the melting transition temperature of fenoverine. This indicated that fenoverine drug was in pure state fig. 2.

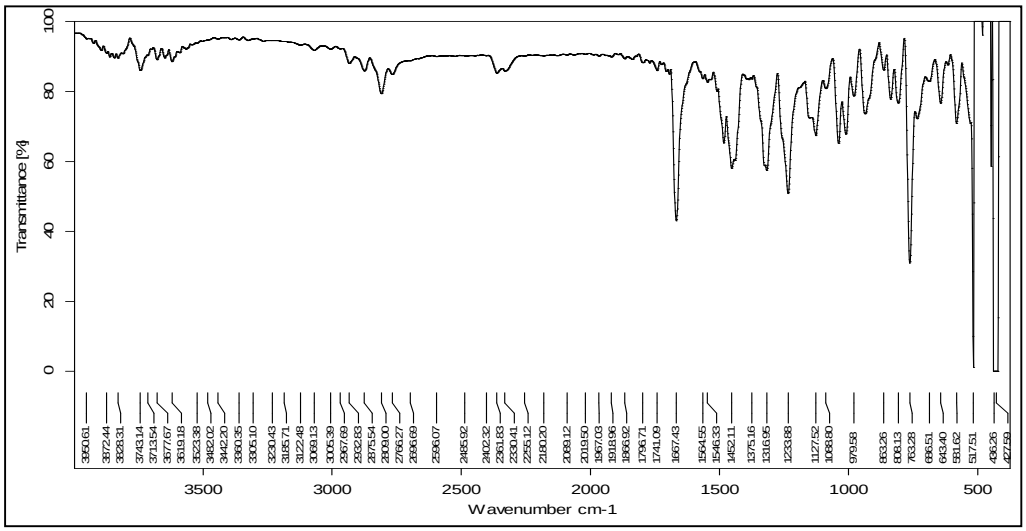

Fig. 1: FTIR spectrum of fenoverine
Note-sample size 5 mg

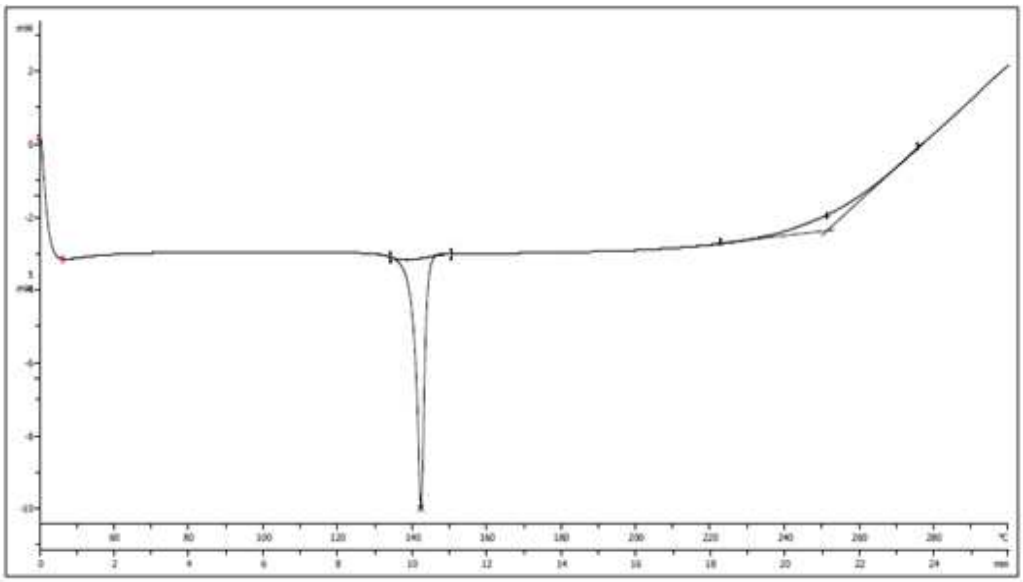

Fig. 2: DSC thermogram of fenoverine
Note-Sample size 2 mg

Drug–polymer compatibility study

FTIR study

The IR spectra of pure drug and formulations were found similar with each other. The main absorption bands of the drug appeared in the formulation spectra shown in table 2**,** fig. 3, 4, 5. It was proved that the peaks found in pure drug and formulations are similar. Thus incorporation of drug in polymer did not change the position of its functional groups. This indicated that there was no difference between the internal structures and conformation of these samples at the molecular level. Hence FTIR study ruled out any possible interaction between drug and polymer.

DSC study

DSC thermogram of formulations containing pullulan, HPMC K4M and HPMC K100M fig. 6, 7, 8 showed a peak at 137.52 °C, 141.14 °C and 140.76 °C respectively. There was no any significant shifting in the peaks of the drug, so it indicated that there was no any interaction between drug and formulation excipients in all thermogram.

Table 2: FTIR spectra of fenoverine and formulations

S. No.	Standard wave number fenoverine [cm^{-1}]	Observed wave number fenoverine [cm^{-1}]	Formulation containing pullulan [cm^{-1}]	Formulation containing HPMC K4M [cm^{-1}]	Formulation containing HPMC K100M [cm^{-1}]	Functional groups associated
1	2810	2808.73	2807.20	2808.08	2810.96	C-H Stretch
2	2973	2964.65	2968.26	2923.14	2967.26	C=C-H Stretch
3	2930	2931.26	2920.84	2923.84	2927.31	C-C-H Stretch
4	1672	1670.07	1668.06	1667.24	1668.50	-C=O Stretch
5	1042	1038.46	1032.24	1035.72	1035.00	C-N Stretch [Aliphatic amines]
6	1238	1234.24	1235.54	1234.08	1234.40	C-N Stretch [Aromatic amines]

Note-cm^{-1}-per centimeter, HPMC-hydroxy propyl methyl cellulose

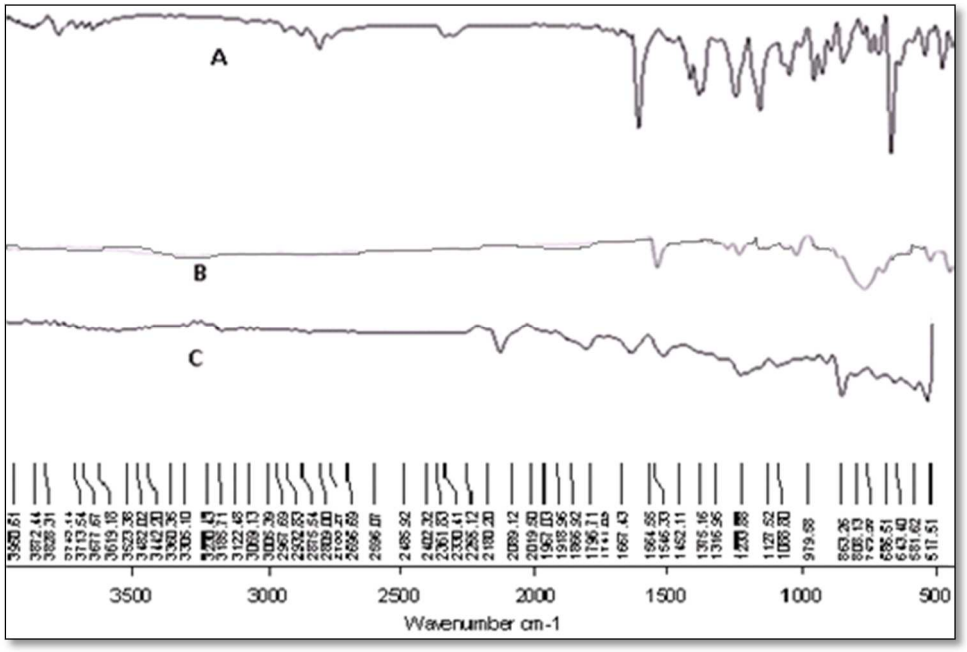

Fig. 3: FTIR spectra of A] Fenoverine B] Pullulan C] Formulation containing pullulan

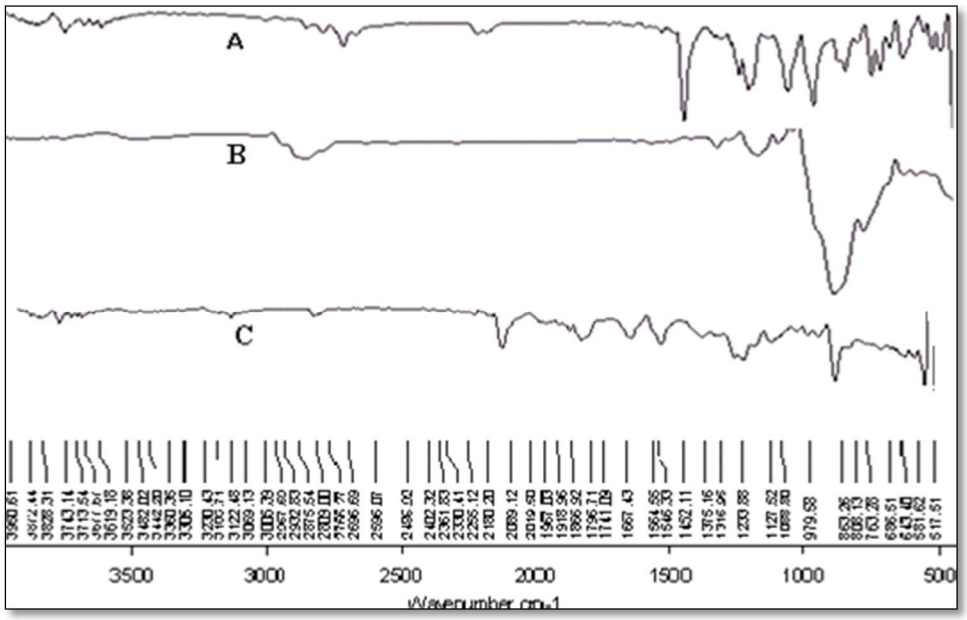

Fig. 4: FTIR spectra of A] Fenoverine B] HPMC K4M C] formulation containing HPMC K4M

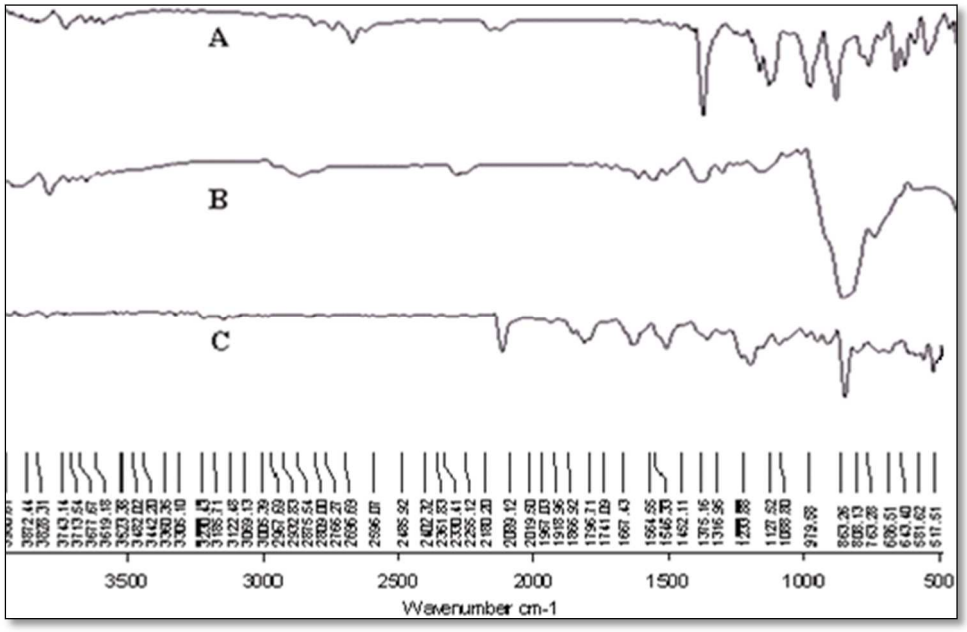

Fig. 5: FTIR spectra of A] Fenoverine B] HPMC K 100M C] formulation containing HPMC K100M

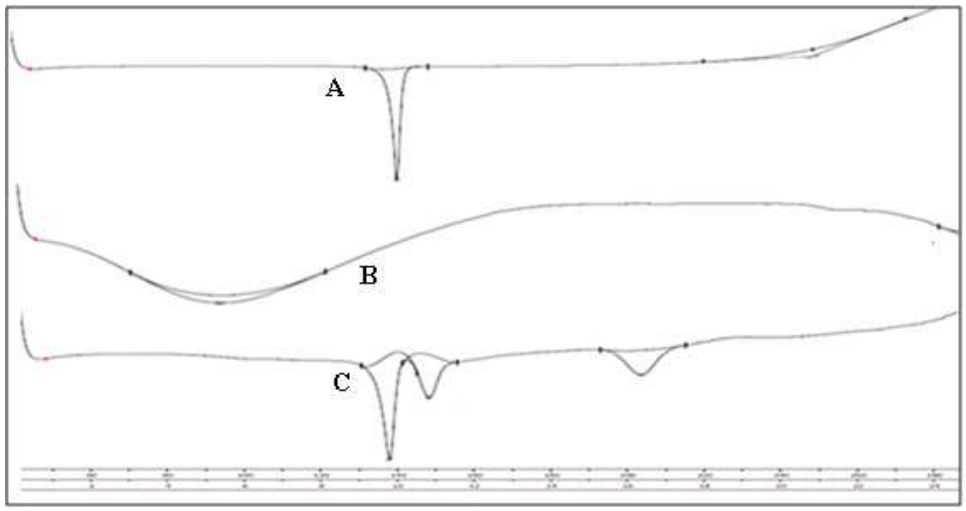

Fig. 6: DSC thermogram of A] Fenoverine B] Pullulan C] formulation containing pullulan

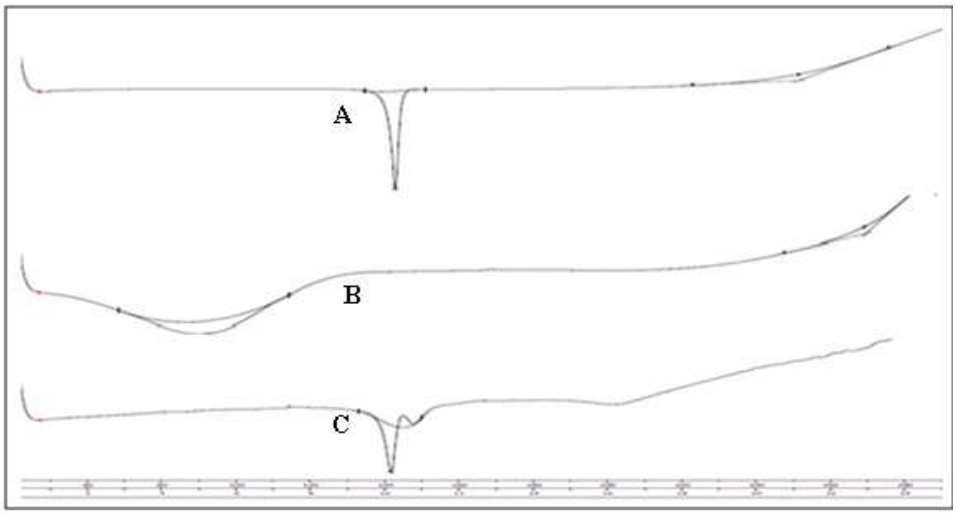

Fig. 7: DSC thermogram of A] Fenoverine B] HPMC K4M C] formulation containing HPMC K4M

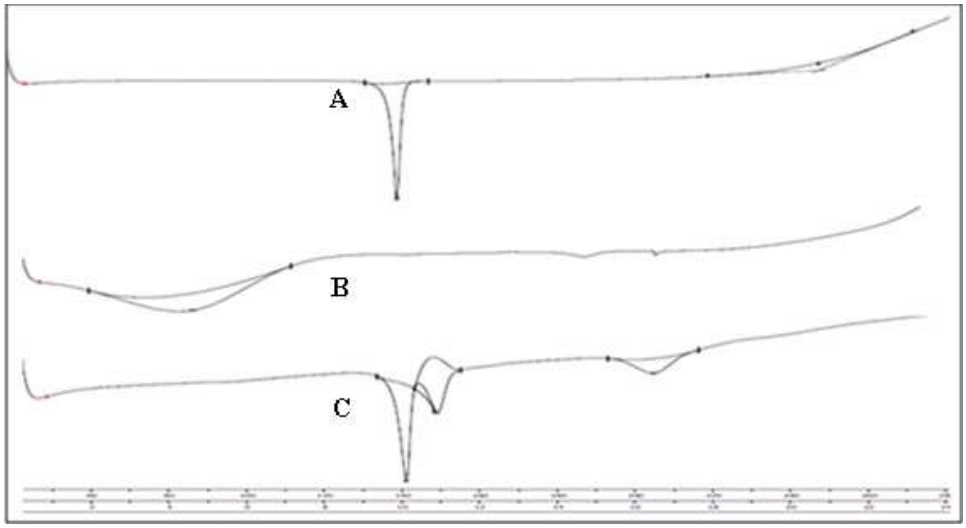

Fig. 8: DSC thermogram of A] Fenoverine B] HPMC K100M C] formulation containing HPMC K100M

Evaluation of tablets

Hardness and thickness

Hardness of tablets from all batches was found to be in the range of 4.5±0.003 kg/cm^{2}to 4.9±0.006 kg/cm^2. All tablets were found hard enough so that they could easily withstand the handling and storage conditions without getting broken. Thickness of tablets ranged from 2.1447±0.02 to 2.2866±0.13 mm. This indicated [1] uniform die fill [2] uniform density [3] compression pressure applied was uniform and [4] drug particles have uniform size and shape.

Friability

All the tablets exhibited acceptable friability as none of the tested batches showed percentage friability that exceeded 1%. As per IP, % friability below 1% is an indication of good mechanical resistance of the tablets. % friability of all batches found in the range of 0.61%-0.78 %. Thus, it was proved that tablets could withstand the pressure, mechanical shocks during handling, transportation, storage and manufacturing processes.

Weight variation test

Weight variation test showed that all tablets were found within the range of 494.7 mg–497.45 mg. None of the tablets deviated from the stated specification i.e.±5%. It is in the limits specified by IP [22]. This indicated uniform flow property, die fill and compression pressure.

Drug content

Drug content of all the formulation batches was found to be between 95.7±0.002 to 99.69±0.004. Hence, it can be concluded that all the formulations are having accurate amount of drug distributed uniformly in powder mass and followed acceptable limits as per IP [22]. i.e. 85 to 115 % of average content table 3.

Table 3: Evaluation parameters of tablets

Batches	Thickness* [mm]	Hardness* [kg/cm^2]	Friability [%]	Average Weight [mg]	Drug content [%]
F1	2.227±0.09	4.955±0.05	0.65	496.63	98.3±0.003
F2	2.227±0.07	4.933±0.07	0.75	497.45	96.74±0.003
F3	2.278±0.11	4.955±0.07	0.78	497.26	95.7±0.002
F4	2.257±0.14	4.935±0.05	0.65	495.76	96.4±0.001
F5	2.286±0.13	4.733±0.21	0.68	494.7	96.69±0.004
F6	2.198±0.04	4.6±0.17	0.66	496.32	99.11±0.003
F7	2.147±0.02	4.622±0.21	0.61	495.99	99.24±0.001

* mean±SD [n = 3]

***In–vitro* release study**

The results of *in–vitro* dissolution study given in table 4 and in fig. 9, it was observed that an increase in polymer concentration from 24 to 30% (F1-F2 and F3-F4) and from 24 to 36 % (F5 to F7) there is a decrease in release rate. The drug release from formulations containing HPMC K100M (F3-F4) was found to be less as compared to other formulations. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retards the drug release from the tablet. Whereas formulations containing pullulan [F5-F7] gave higher drug release as compared to other formulations, which may be due to quick hydration and erosion of polymer matrix. As compared pullulan, HPMC polymers are less hydrophilic and require more time to get hydrated. In addition to the concentration of polymer matrix, the type and viscosity of polymer also influence on drug release.

In–vitro dissolution study data shows cumulative drug release was in the order like F5>F1>F6>F2>F7>F3>F4. This might be due to the nature, viscosity and concentration of the various polymers used. Pullulan has powerful retardant property resulting in a matrix formation which is required for sustained release formulations. The data also indicated that because of quick hydration and erosion of pullulan polymer there was more drug release in 2 h, 4 h, 6 h etc. as compared to HPMC polymers. Formulation F5 was considered as optimized formulation as it showed highest cumulative % drug release i.e. 96.82±0.75 % at the end of 12 h.

The tablets with pullulan polymer showed comparative dissolution profile with tablets with HPMC polymers and showed drug release rate retarding properties.

Kinetics of *in vitro* drug release

The *in vitro* release data obtained were fitted into various kinetic models Optimized batch F5 showed case II transport mechanism [n>1] i.e. drug transport mechanism associated with stresses and

state transition in hydrophilic glassy polymers which swell in water or biological fluids, also includes polymer disentanglement and erosion and followed zero order release pattern showed in table 5. So, predominant drug release mechanism is controlled release.

Table 4: *In vitro* dissolution study

Time [H]	% CDR*						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	1.89±0.14	6.45±0.13	5.73±0.7	3.07±0.48	12.89±0.73	8.54±0.55	11.92±0.72
2	7.29±0.46	10.14±0.42	12.26±0.25	11.64±0.91	19.74±0.64	13.21±0.3	14.88±1.25
3	11.03±0.12	13.19±0.39	15.89±0.38	11.84±0.62	25.68±1.22	17.38±0.66	18.72±0.53
4	13.73±0.59	16.33±0.64	20.61±0.58	16.42±0.91	33.07±0.6	19.89±0.74	21.63±0.92
5	17.67±0.4	18.39±0.42	23.96±0.49	20.56±1.22	43.71±0.17	24.76±0.56	25.5±0.27
6	21±0.19	22.77±0.48	31.44±0.33	30.75±0.74	54.04±0.5	29.21±1.13	39.16±0.23
7	31.49±0.32	40.34±0.6	40.06±0.18	43.78±0.65	62.21±0.76	36.06±1.11	43.58±0.52
8	49.13±0.26	54.38±0.59	52.82±1.06	53.5±0.55	69.42±0.41	48.41±0.38	49.94±0.98
9	53.89±0.21	67.59±0.31	60.38±0.3	60.99±0.78	77.05±0.64	56.74±0.9	62.19±0.69
10	61.52±0.23	72.62±0.47	67.51±0.48	67.47±0.98	83.09±0.16	66.48±0.79	66.51±1.18
11	67.32±0.23	75.5±0.51	73.44±1.47	71.95±1.12	88.27±0.57	74.18±1.04	79.68±0.14
12	88.62±0.16	85.34±0.92	80.12±0.8	78.12±0.99	96.82±0.75	85.96±0.69	83.77±0.42

* mean±SD [n = 3]

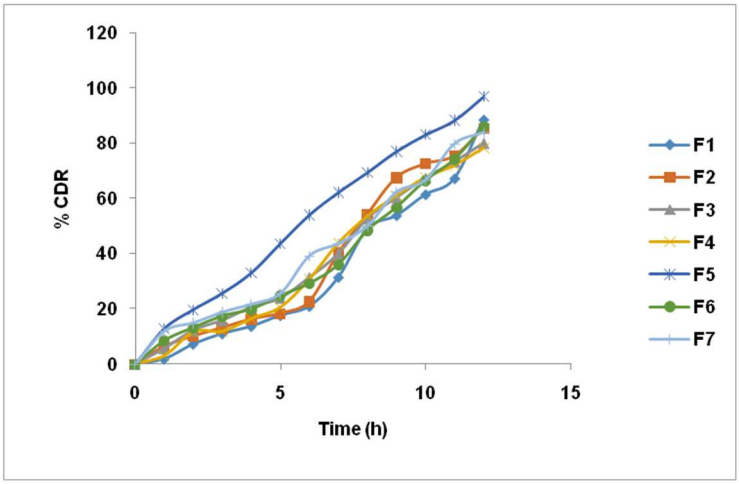

Fig. 9: *In vitro* drug release profile of formulations F1 to F7
Note-error bars omitted

Table 5: Study of various kinetic models

Batch	Zero order	First order	Higuchi	Hixson-Crowell	Korsemeyer-peppas		Best fit model
	r^2	r^2	r^2	r^2	r^2	n	
F1	0.946	0.696	0.869	0.939	0.973	1.889	K-peppas
F2	0.942	0.957	0.872	0.968	0.985	1.700	K-peppas
F3	0.983	0.902	0.933	0.969	0.992	1.636	K-peppas
F4	0.973	0.782	0.928	0.928	0.928	1.736	K-peppas
F5	0.994	0.920	0.976	0.960	0.983	1.594	Zero order
F6	0.958	0.979	0.882	0.994	0.983	1.606	H. Crowell
F7	0.955	0.982	0.880	0.992	0.979	1.601	H. Crowell

Stability studies

Short-term stability studies of the optimised formulation indicated that there were no significant changes in hardness, drug content and *in vitro* dissolution studies at the end of three months period table 6, 7, and fig. 10, $P < 0.05$. Similarity factor *f2* of dissolution profiles of optimized formulation F5 before and after stability study was found to be 89, which indicated similar dissolution profiles before and after stability study.

Table 6: Stability study data of formulation F5

Parameters	0 Mo	1 Mo	2 Mo	3 Mo
Hardness*[kg/cm^2]	4.7±0.2	4.7±0.2	4.6±0.1	4.6±0.1
Drug content* [%]	99.69±0.004	99.57±0.01	98.59±0.09	98.21±0.09

*mean±SD [n = 3]

Table 7: *In vitro* dissolution study of formulation F5 before and after stability

Time [H]	Cumulative % drug release at			
	0 Mo	1 Mo	2 Mo	3Month
0	0	0	0	0
1	12.89±0.73	12.80±0.01	12.44±0.31	12.10±0.11
2	19.74±0.64	19.55±0.5	19.41±0.26	18.45±0.01
3	25.68±1.22	25.39±0.37	25.23±0.01	24.50±0.33
4	33.07±0.6	33.00±0.53	32.84±0.13	32.06±0.05
5	43.71±0.17	43.56±0.45	43.25±0.17	42.30±26
6	54.04±0.5	54.11±0.09	53.98±0.01	53.16±0.01
7	62.21±0.76	62.1±0.11	61.94±0.06	61.06±0.07
8	69.42±0.41	69.09±0.12	68.79±0.27	68.20±0.13
9	77.05±0.64	76.86±0.15	76.35±0.13	75.24±0.07
10	83.09±0.16	83.09±0.01	82.97±0.01	81.17±0.05
11	88.27±0.57	88.11±0.01	87.77±0.27	86.13±0.01
12	96.82±0.75	96.42±0.20	95.30±0.12	94.63±0.26

* mean±SD [n = 3]

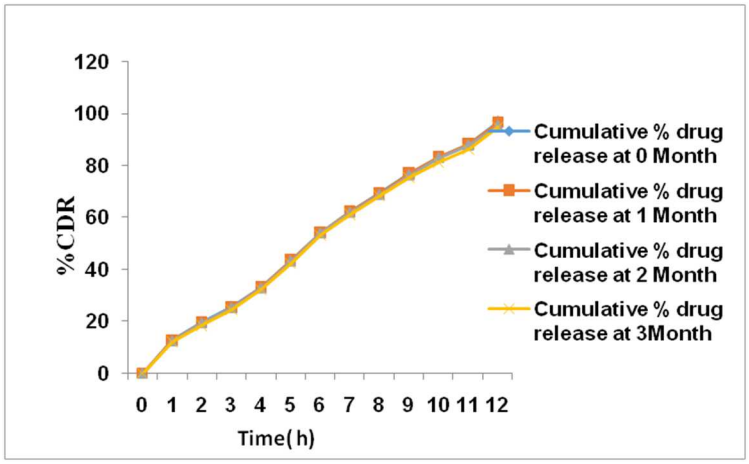

Fig. 10: Dissolution profile of formulation F5 before and after stability study
Note-error bars omitted

CONCLUSION

Fenoverine controlled release matrix tablets were prepared by using different concentrations of pullulan, HPMC K4M and HPMC K100M by direct compression method and evaluated. FTIR and DSC studies indicated that there were no drug-excipients interactions. *In vitro* drug release study showed that, as the amount of polymer increases, the drug release decreases. Optimized batch F5 showed case II transport mechanism and followed zero order release kinetics. Short-term stability studies of the optimized formulation indicated that there was no significant change observed in hardness, drug content and *in vitro* dissolution studies. Similarity factor *f2* was found to be 89, which indicated similar dissolution profiles before and after stability study. Pullulan a novel natural polymer showed drug release controlling characteristics. Hence it can be concluded that pullulan can be used as a polymer for retarding the release of drug from matrix formulations.

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CONFLICTS OF INTERESTS

Declare none

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