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Formulation and Evaluation of Sustained Released Metformin HCl Tablet Using Natural Polymers

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ABSTRACT

Metformin HCl matrix tablets were formulated and evaluated using different drug polymer (pectin/alginate) by direct compression method. The blends were evaluated for precompression and postcompression studies including Swelling & erosion studies. *In vitro* release studies were carried out in acidic buffer (pH1.2) and phosphate buffer (pH 6.8). The drug release was found to decrease with increase in the amount of polymer added in each formulation. Release studies also showed that the swelling and erosion of matrix tablets influenced the drug release and a bi-phasic release with an initial burst effect was observed with matrix tablets. The percent cumulative drug release was found to be sustained for all formulations and best formulation was A3 with 94.16% drug release in 11hrs. The kinetic studies revealed that the three formulations were good fitted into Korsmeyer-Peppas and six formulations were good fitted in Higuchi matrix model.

INTRODUCTION

In the last few years, diabetes has reached epidemic proportion and now becoming cause of premature mortality and morbidity. Some antidiabetic drug like Metformin HCl, having short half-life make them suitable candidate to be formulated as sustained-release drug delivery system[1] to ensure safety and to improve efficacy of drugs[2] as well as patient compliance, which can be achieved by better control of plasma levels and less frequent dosing.[3]

Hydrophilic matrix tablets are a well known type of sustained-release formulation for oral administration[4] and being increasingly investigated for sustained release applications because of their good compatibility as well as they are easy and economical to formulate.[5] Pectin, a natural polymer is structural component of plant cell wall. The non-toxicity and low production costs make them great interest for the formulation of sustained release as it rapidly forms viscous solution and gels on contact with aqueous media.[6] Matrices including pectin have been employed for the prolong-release of many drugs.[7] Alginates, which are commonly available as sodium salt, are a natural polymer having high biological safety and properties to form viscous solutions and gels on contact with aqueous media can be used as hydrophilic matrix for sustained-release of oral dosage form.[8]

Therefore this study is aimed to investigate the effect of various blends of pectin / alginate on swelling, erosion and drug release from matrix tablets.

Natural polymers are much safer than synthetic. They provide many applications in the formulation development of a new controlled release dosage form, such as binder, disintegrator, diluents and release modifier. Therefore, they needs a novel approach to enhance the use of natural polymer in the formulation development of controlled release dosage form, because of the ease availability at an affordable price, high safety margin and higher productivity.[9,10,11] In drug administration, controlled release dosage forms offer numerous advantages compared to conventional immediate release dosage forms, including potential for greater effectiveness in the treatment of chronic conditions through more predictable kinetics, reduced side effects and toxicity by minimizing peak plasma concentrations, greater convenience and higher levels of patient compliance due to simplified dosage schedule.[12]

MATERIALS AND METHODS

Materials

Metformin HCl, Pectin, Sodium alginate, Sodium stearyl fumarate, Talc, Potassium dihydrogen phosphate, Sodium hydroxide, Potassium Chloride, Hydrochloric acid. The given materials were either AR/LR or the best possible grade available, were used as supplied by the manufacturer without further purification or investigation.

STANDARD CALIBRATION CURVE

Most drugs absorb light in the ultraviolet wavelengths (190-390nm), since they are generally aromatic or contain double bonds.

Determination of λ_{max} of Metformin HCl [13]

The λ_{max} of Metformin HCl was determined in pH 1.2 acid buffer, in pH 6.8 phosphate buffer and distilled water. The various drug concentrations prepared in the determination of calibration curve were used to check the λ_{max} of Metformin HCl. The λ_{max} of Metformin HCl in pH 1.2 acid buffer, pH 6.8 phosphate buffer and distilled water was found to be 233nm.

FORMULATION OF MATRIX TABLETS [14,15]

Matrix tablets were prepared by direct compression method. Different blends of pectin and sodium alginate with Metformin HCl were prepared and then all ingredients were passed through a 60-mesh sieve. All the ingredients were mixed thoroughly for 15 minutes without additives and for a further 5 minutes after addition of additives.

Sodium stearyl fumarate was used as a lubricant and talc was used as a glidant.

1. Pectin as a polymer showing drug: polymer ratios from 3.3:1 (P1), 2.5:1 (P2), 2:1 (P3).
2. Sodium alginate as a polymer showing drug: polymer ratios from 3.3:1 (A1), 2.5:1 (A2), 2:1 (A3).
3. Pectin and sodium alginate as polymers showing drug: polymer ratios from 3.3:0.5:0.5 (PA1), 2.5:0.5:0.5 (PA2), 2:0.5:0.5 (PA3).

Tablets were prepared by using 12mm diameter die- punch set on tablet compression machine (10 station) Kambert (Kambert machinery, Ahmadabad, India).

Table 1. Formulations of Metformin HCl Matrix tablets

Formulation	P1	P2	P3	A1	A2	A3	PA1	PA2	PA3
Metformin	500	500	500	500	500	500	500	500	500
Pectin	150	200	250	-	-	-	75	100	125
Sodium Alginate	-	-	-	150	200	250	75	100	125
Sodium stearyl fumarate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Total weight in mg	670	720	770	670	720	770	670	720	770

EVALUATION OF MATRIX TABLETS[16,17]

FTIR Spectral Studies

FTIR spectral data was taken on a Bruker (Alpha series, Germany) instrument to study the compatibility of formulation. FTIR spectra of formulation were obtained by mixing with KBr to get pellet under a pressure of 600kg/cm^2. Spectral scanning was done in the range between 4000 and 500cm^{-1}.

In Vitro Dissolution Studies

Drug release from the Matrix tablets were investigated using USP XXIII dissolution apparatus (Electrolab, Model TDT 08L, India) equipped with eight paddle at the stirring speed of 50rpm using 900ml pH 1.2 acid buffer solution for the initial 2h, followed by pH 6.8 phosphate buffer solution up to 11hours. The dissolution medium was maintained at 37±0.5˚C. At the interval of 1hour 5ml of the sample was withdrawn from the dissolution media and the same amount was replaced with fresh buffer to maintain the sink conditions. The concentration of Metformin HCl was determined using a UV spectrophotometer at the λ_{max} of 233nm. These studies were performed in triplicate for each sample.

Swelling and Erosion Studies[18]

The metallic baskets containing a matrix tablet was weighed (initial weight W0) and placed in 900ml of acidic buffer (pH 1.2) for initial 2hours followed by phosphate buffer (pH 6.8) upto 10hours in Orbital Shaker Incubator (BIO BEE Tech, Bangalore, India) at 37.0±0.5˚C.

At hourly intervals, the previously weighted baskets with the tablet were removed, gently wiped with a tissue to remove surface water, re-weighted (W1). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from the following equation:

$$\% \text{ weight change} = W1 - W0 / W0 \times 100$$

Matrix erosion studies were performed after the swelling studies, the wet samples were then dried in an oven at 80˚C for 24-h time period, allowed cooling in desiccators and finally weighed until constant weight was achieved (final dry weight, W2). The experiment was performed in triplicate for each time point. The tablet erosion (ES) at different times was estimated from the following equation:

$$ES = W0 - W2 / W0 \times 100$$

The percentage weight remaining of tablets after erosion was calculated from the following equation:

$$\% \text{ weight remaining} = 100 - ES$$

Figure 1. Image of tablets of formulation P1, P2, P3, A1, A2, A3, PA1, PA2, PA3

RESULTS AND DISCUSSION

Standard Calibration Curve

Determination of λ_{max} of Metformin HCl

Absorption spectrum of pure drug was scanned between 200-400nm prepared in distilled water, pH 1.2 acidic buffer and pH 6.8 phosphate buffer solution. The absorption maxima were found to be at 233nm in all the solutions and spectra is presented in Figure 2.

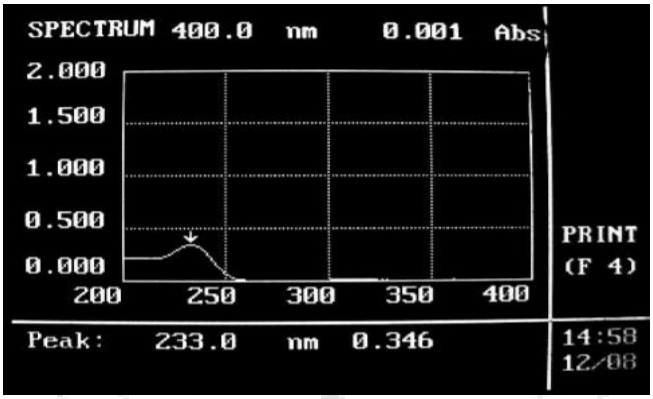


Figure 2. Standard calibration curve of Metformin HCl: λ_{max} of Metformin HCl

Figure 2 shows the absorbance of standard solutions of ranging from 2-12µg/ml in different buffers. g/ml in different buffers. Figure 2.1, 2.2 & 2.3 shows Standard calibration curve.

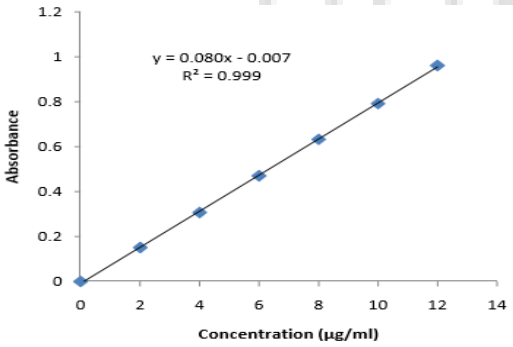


Figure 2.1 Standard calibration curve of Metformin HCl in pH 1.2 acidic buffer

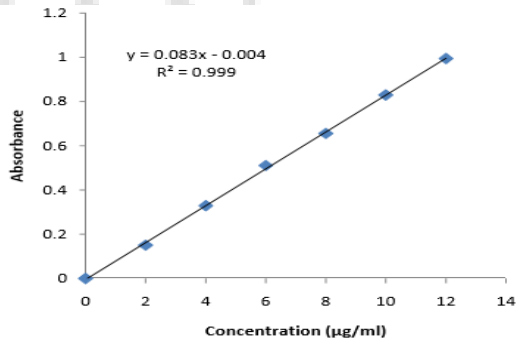


Figure 2.2 Standard calibration curve of Metformin HCl in pH 6.8 phosphate buffer

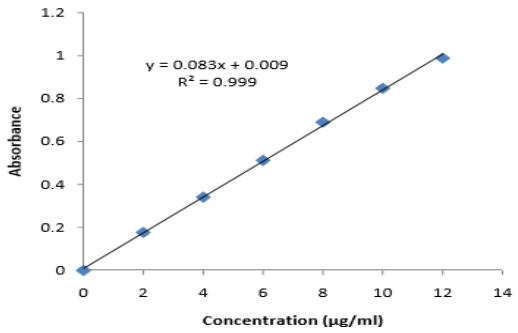


Figure 2.3 Standard calibration curve of Metformin HCl in Distilled water

Table 3. Absorbance values of Metformin HCl for standard calibration curve

Sr. No.	Concentration (µg/ml)	Absorbance* at 233nm		
		pH 1.2	pH 6.8	Distilled water
1	2	0.151	0.151	0.177
2	4	0.307	0.329	0.341
3	6	0.470	0.511	0.512
4	8	0.633	0.656	0.690
5	10	0.792	0.829	0.848
6	12	0.961	0.944	0.988

*Mean of three determinations

In preformulation studies, it was found that, the estimation of Metformin HCl by spectrophotometric method at 233nm in pH 1.2 acidic buffer, pH 6.8 phosphate buffer and distilled water had good reproducibility at the concentration between 2-12µg/ml. Correlation between concentration and absorbance was found to be closer to 1.0.

Table 4. Precompression data

Formulations	Angle of repose (Degrees)*	Bulk density (gm/ml)*	Tapped density (gm/ml)*	Carr's index (%)*	Hausner ratio*
P1	33.24	0.56	0.67	16.41	1.19
P2	32.05	0.54	0.68	20.48	1.25
P3	31.36	0.59	0.72	18.05	1.22
A1	34.44	0.56	0.75	25.33	1.33
A2	33.16	0.55	0.64	14.06	1.16
A3	34.41	0.57	0.66	13.63	1.15
PA1	31.55	0.56	0.69	18.84	1.23
PA2	32.47	0.57	0.73	21.91	1.28
PA3	33.68	0.59	0.71	16.90	1.20

*Mean of three determinations

Total weight taken 25gm for tests

No. of strokes 100 for tapped density

Table 4 shows precompression data of the formulations. Angle of repose was found between 31.36 to 34.44 degrees, bulk density was found between 0.54 to 0.59(gm/ml), Tapped density was found between 0.64 to 0.75(gm/ml), Carr's index was found between 13.63 to 25.33% and Hausner ratio was found between 1.15 to1.33

EVALUATION OF MATRIX TABLETS

-FTIR Spectral Studies

Drug-Excipients compatibility study

Compatibility study of drug in formulation was conducted by employing FTIR Spectrum.

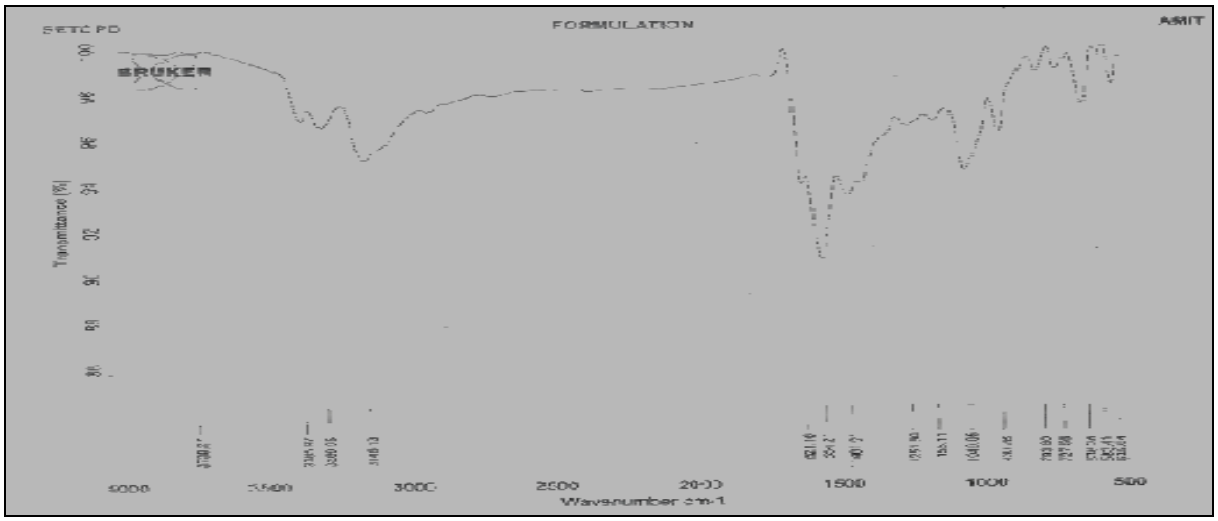


Figure 3. FTIR spectrum of Formulation

Table 5. Characteristics of different functional groups of Metformin HCl in formulation

Characteristic	**Energy (Cm -1)**
-NH_2 stretching	3371
-NH stretching	3293
N-H deformation and asymmetric NCN stretching	1623, 1559
CH_3 asymmetric and symmetric deformation	1446
C-N stretching and CH_3 rocking	1057, 934

Comparison of FTIR spectra of pure drug and formulation showed the presence of all the characteristic peaks of drug in the formulation indicating the chemical stability of the drug in the formulation. Thus, FTIR spectral studies indicated the absence of interactions between drug and excipients.

POSTCOMPRESSION DATA

Table 6. Post compression data

Formulations	Diameter (mm)	Thickness (cm), n=3	Hardness (kg/cm^2), n=3	Weight (mg), n=20	Friability (%), n=3	Drug Content (%), n=3
P1	12	0.578±0.004	5.46±0.11	669.35±5.97	0.73	99.35±1.13
P2	12	0.625±0.002	4.86±0.13	719.30±7.42	0.87	98.95±0.97
P3	12	0.668±0.001	4.73±0.08	769.35±6.19	0.78	98.47±0.13
A1	12	0.594±0.002	5.66±0.14	670.60±5.18	0.65	99.27±0.83
A2	12	0.624±0.004	5.26±0.12	719.45±7.52	0.64	99.11±0.69
A3	12	0.647±0.021	4.93±0.07	769.15±6.70	0.72	99.19±0.91
PA1	12	0.582±0.002	5.46±0.21	670.05±5.85	0.69	98.71±0.36
PA2	12	0.626±0.003	4.93±0.09	720.10±6.76	0.68	99.43±1.41
PA3	12	0.656±0.002	4.66±0.23	769.20±6.82	0.71	99.03±1.34

n indicates no of determinations.

Post compression studies were carried out and the data are given in Table 6. Weight, friability and drug contents of the tablets are found to be complied with the standards.

IN VITRO DRUG RELEASE

Table 7
***In vitro* Drug release of formulation P1, P2, P3**

S. No.	Time (hr)	% Cumulative drug release (Mean±S.D.)		
		P1	P2	P3
1	0	0	**0**	**0**
2	1	35.18±0.89	31.77±0.44	26.44±0.44
3	2	47.89±0.67	41.44±0.67	37.28±0.25
4	3	54.88±0.33	50.61±0.37	46.62±0.76
5	4	64.99±0.43	56.01±0.25	54.19±0.33
6	5	68.32±0.65	67.21±0.43	62.92±0.54
7	6	75.77±0.37	76.46±0.54	70.80±0.12
8	7	82.36±0.22	79.51±0.57	80.13±0.21
9	8	87.80±0.33	86.68±0.33	86.66±0.12
10	9	94.83±0.50	93.21±0.33	88.99±0.21
11	10	99.85±0.12	96.21±0.54	91.84±0.54
12	11	99.96±0.74	98.12±0.21	95.84±0.62

n=3

Figure 4
***In vitro* Drug release of Formulation P1, P2, P3**

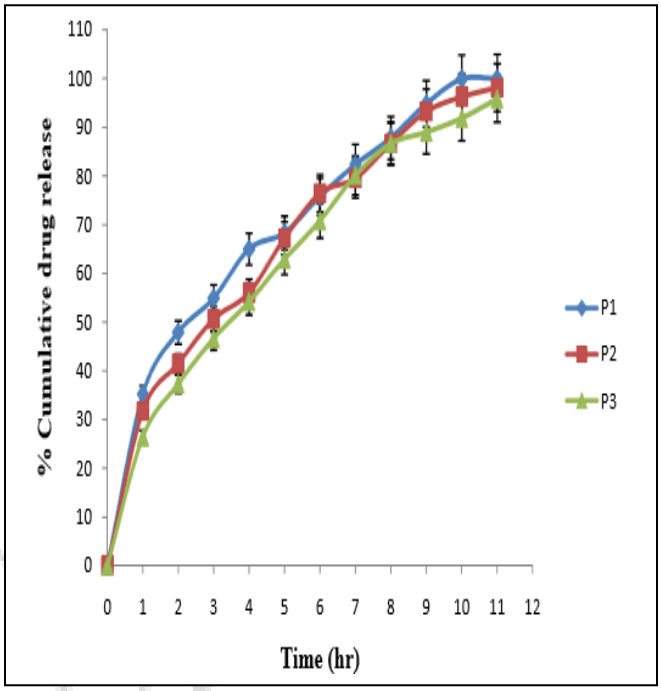


Table 8
***In vitro* Drug release of formulation A1, A2, A3**

Sr. No.	Time (hr)	% Cumulative drug release (Mean±S.D.)		
		A1	A2	A3
1	0	0	0	0
2	1	28.07±0.13	29.55±0.58	23.62±0.12
3	2	43.43±0.33	39.36±0.44	35.06±0.14
4	3	53.64±0.21	49.45±0.12	48.06±0.33
5	4	62.16±0.21	61.36±0.33	55.85±0.43
6	5	69.09±0.12	67.13±0.12	61.12±0.21
7	6	73.65±0.66	71.40±0.21	67.91±0.65
8	7	81.54±0.33	79.94±0.57	77.45±0.33
9	8	86.62±0.45	84.51±0.25	83.61±0.33
10	9	94.23±0.21	86.26±0.12	87.39±0.12
11	10	98.89±0.21	93.23±0.22	91.17±0.26
12	11	99.29±0.75	96.44±0.49	94.16±0.63

Figure 5
***In vitro* Drug release of formulation A1, A2, A3**

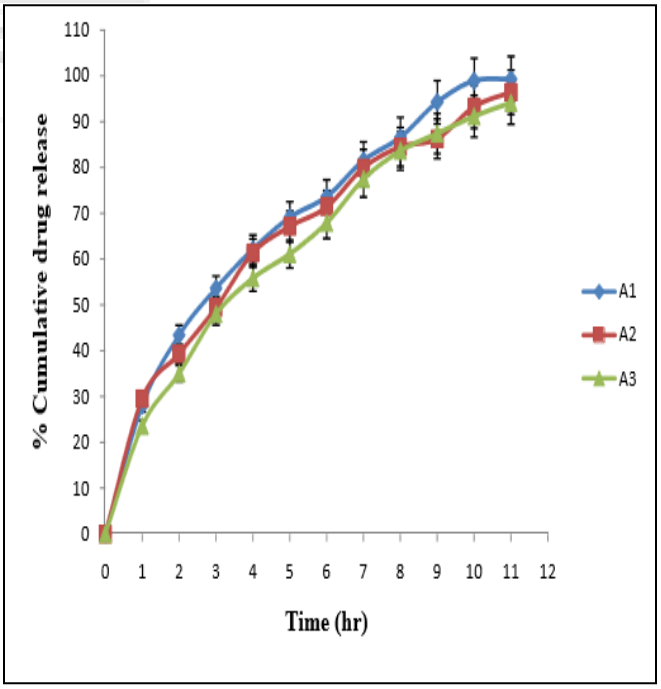
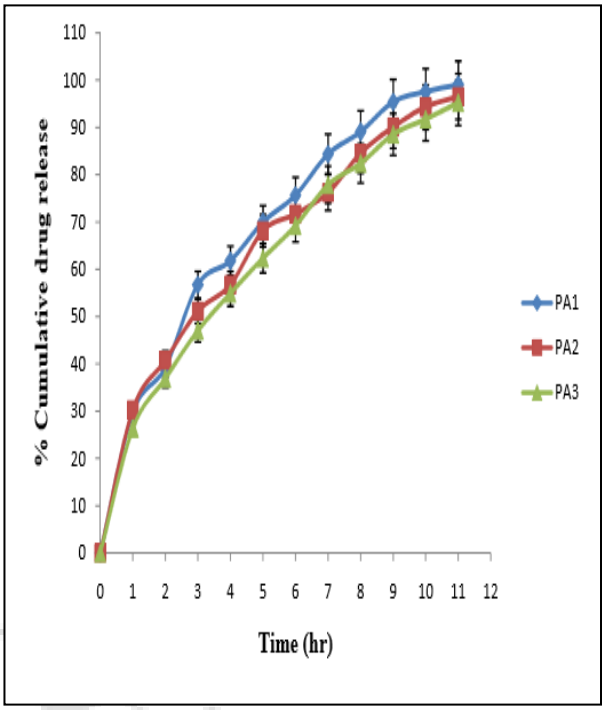


Table 9
***In vitro* Drug release of formulation PA1, PA2, PA3**

Sr. No.	Time (hr)	% Cumulative drug release (Mean±S.D.)		
		PA1	PA2	PA3
1	0	0	0	0
2	1	29.70±0.46	30.29±0.55	26.29±0.92
3	2	39.21±0.33	40.70±0.48	36.84±0.67
4	3	56.75±0.12	51.11±0.45	46.98±0.33
5	4	61.80±0.25	56.73±0.21	54.91±0.54
6	5	69.96±0.25	68.15±0.33	62.35±0.97
7	6	75.68±0.25	71.69±0.36	69.21±0.65
8	7	84.36±0.33	76.25±0.43	77.89±0.76
9	8	89.08±0.87	84.58±0.37	82.39±0.99
10	9	95.40±0.42	90.09±0.62	88.55±0.87
11	10	97.53±0.29	94.31±0.43	91.76±0.66
12	11	99.08±0.65	96.51±0.29	95.18±0.74

n=3

Figure 6
***In vitro* Drug release of formulation PA1, PA2, PA3**



The release data obtained from the formulations are mentioned in Table 7, 8, 9 and Figure 4, 5, 6.

It was observed that the drug release from the formulations decreased with increase in the amount of polymer added in each formulation. The release showed a bi-phasic release with an initial burst effect. In the first hour drug release was 35.18%, 31.77%, 26.44%, 28.07%, 29.55%, 23.62%, 29.70%, 30.29% and 26.29% for P1, P2, P3, A1, A2, A3, PA1, PA2 and PA3 formulations respectively. The mechanism for the burst release can be attributed to initial wetting of the polymers cause swelling of outer layer of the tablets.

The overall cumulative % drug release for P1, P2, P3, A1, A2, A3, PA1, PA2 and PA3 were found to be 99.96%, 98.12%, 95.84%, 99.29%, 96.44%, 94.16%, 99.08%, 96.51% and 95.18% respectively at the end of 11th hour.

In the pectin formulations the drug: polymer ratio 2:1(P3) showed slower drug release as compared to 3.3:1(P1) and 2.5:1(P2). From Sodium alginate formulations drug polymer: ratio with 2.5:1(A2) and 2:1(A3) showed slower drug release than 3.3:1(A1). In the formulations,

where mixture of both polymers is used with drug: polymer ratio 2.5:0.5:0.5(PA2) and 2:0.5:0.5(PA3) showed slower drug release than 3.3:0.5:0.5(PA1).

SWELLING AND EROSION STUDIES

The water uptake (swelling) and erosion studies were carried out for all formulations. The results of these tests are provided as the percentage weight change and percentage weight remaining of tablet mass. The swelling behavior indicated the rate at which this formulation absorbed water from dissolution media and swelled. The percentage Weight remaining of the matrices reflects the amount of polymer dissolved and the erosion of matrix during process. Table 10, 11, 12, 13, 14 & 15 showed swelling and erosion data for the formulations.

Table 10
Swelling data of formulation P1, P2, P3

Sr. No.	Time (hr)	% Cumulative drug release (Mean±S.D.)		
		P1	P2	P3
1	0	0	0	0
2	0.5	43.58±0.24	34.87±0.81	38.75±0.24
3	1	56.21±0.58	48.18±0.84	52.84±0.15
4	2	77.02±0.78	70.56±0.67	61.27±0.51
5	3	96.87±0.88	81.41±0.24	73.71±0.21
6	4	104.45±0.90	97.67±0.28	83.54±0.26
7	5	114.21±0.99	105.78±0.71	92.03±0.84
8	6	121.98±1.05	113.75±0.96	100.47±0.14
9	7	125.66±1.08	127.55±0.93	106.85±1.02
10	8	139.89±0.97	131.34±0.81	113.84±0.36
11	9	140.71±0.81	134.49±0.75	118.34±0.38
12	10	141.08±0.31	134.85±0.78	123.60±0.84

n=3

Figure 7
Swelling data of formulation P1, P2, P3

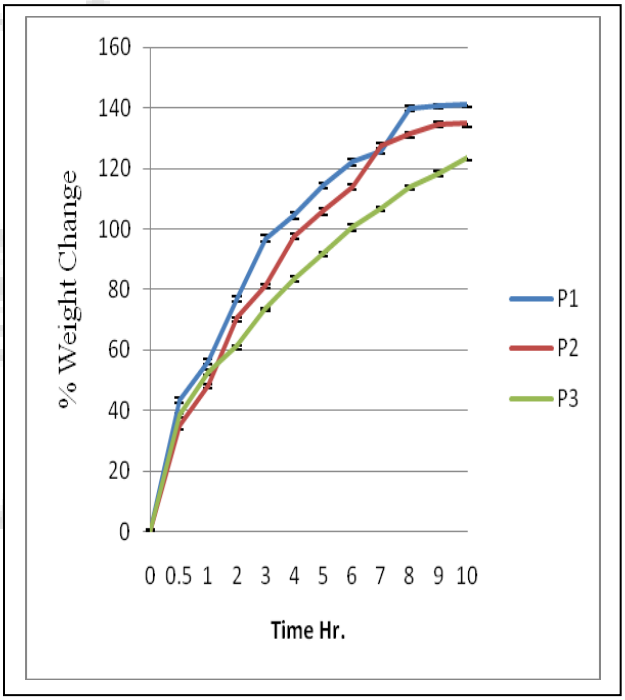


Table 11
Erosion data of formulation P1, P2, P3

Sr. No.	Time (hr)	% Weight remaining (Mean±S.D.)		
		P1	P2	P3
1	0	100	100	100
2	0.5	95.77±0.25	97.38±0.46	96.18±0.65
3	1	92.05±0.51	95.59±0.84	93.25±0.25
4	2	91.85±0.56	90.48±0.15	92.54±0.15
5	3	89.40±0.69	86.55±0.81	89.50±0.53
6	4	84.22±0.81	85.83±0.03	85.64±0.54
7	5	80.44±0.50	82.57±0.84	81.82±0.85
8	6	74.56±0.24	77.05±0.54	79.06±0.57
9	7	68.26±0.14	71.35±0.24	73.02±0.15
10	8	62.17±0.53	64.45±0.25	69.25±0.17
11	9	59.78±0.19	62.18±0.14	65.24±0.66
12	10	51.54±0.36	55.66±1.05	62.67±0.12

n=3

Figure 8
Erosion data of formulation P1, P2, P3

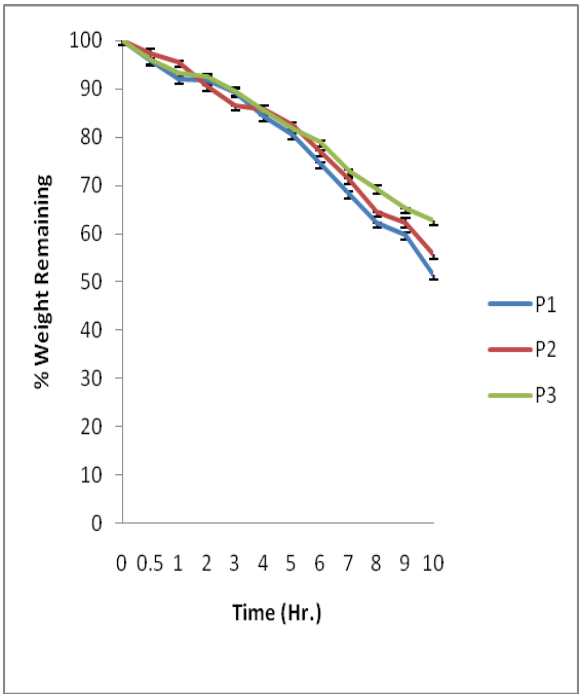


Table 12
Swelling data of formulation A1, A2, A3

Sr. No.	Time (hr)	% Weight change (Mean±S.D.)		
		A1	A2	A3
1	0	0	0	0
2	0.5	41.98±0.71	39.47±0.71	35.47±0.14
3	1	55.14±0.24	54.87±0.83	42.77±1.02
4	2	74.64±0.58	68.23±0.82	64.10±0.25
5	3	92.11±0.63	84.36±0.96	74.31±0.36
6	4	106.47±0.58	95.36±0.98	81.60±0.85
7	5	116.90±0.48	101.74±0.17	90.71±0.75
8	6	124.68±0.36	109.71±0.64	95.82±0.91
9	7	129.71±0.88	115.38±0.39	104.05±0.14
10	8	140.61±0.91	122.01±0.80	108.11±0.29
11	9	142.99±0.87	124.37±0.37	113.99±0.23
12	10	143.11±0.46	129.46±0.51	119.46±0.90

Figure 9
Swelling data of formulation A1, A2, A3

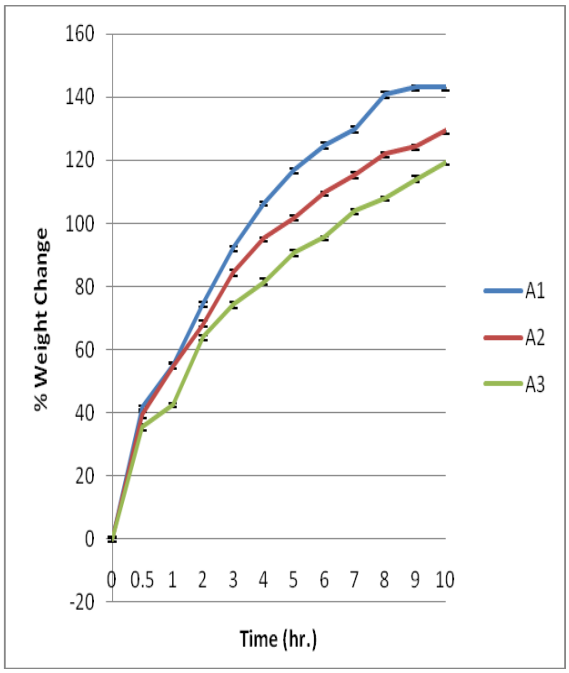


Table 13
Erosion data of formulation A1, A2, A3

Sr. No.	Time (hr)	% Weight remaining (Mean±S.D.)		
		A1	A2	A3
1	0	100	100	100
2	0.5	98.64±0.51	97.91±0.84	99.52±0.14
3	1	95.60±0.41	96.15±0.42	96.92±0.03
4	2	92.84±0.85	93.98±0.64	93.13±0.25
5	3	90.06±0.57	92.70±0.67	89.18±0.27
6	4	88.02±0.18	87.92±0.52	86.40±0.24
7	5	87.88±0.12	85.74±0.83	85.63±0.14
8	6	84.57±0.14	82.81±0.36	82.22±1.05
9	7	83.43±0.11	79.09±0.42	81.06±0.54
10	8	76.38±0.25	74.95±0.15	78.44±0.65
11	9	70.06±1.02	69.54±0.56	76.72±0.98
12	10	64.08±0.28	66.71±0.25	72.45±0.57

Figure 10
Erosion data of formulation A1, A2, A3

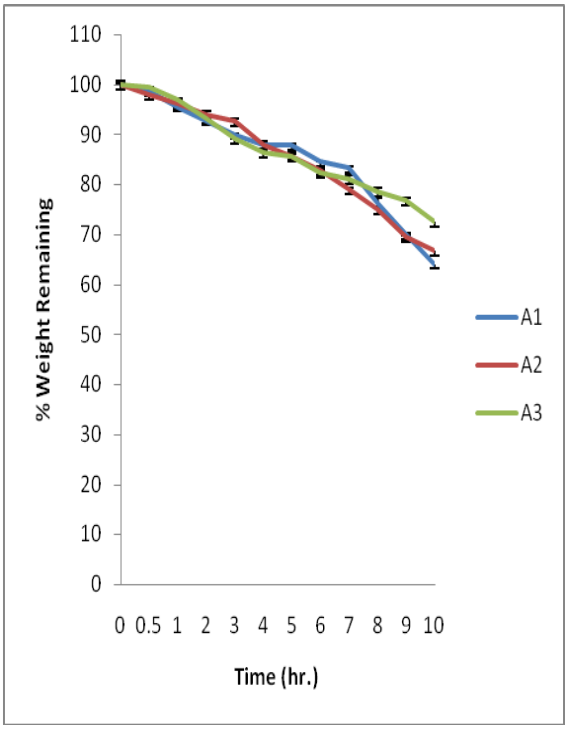


Table 14
Swelling data of formulation PA1, PA2, PA3

Sr. No.	Time (hr)	% Weight change (Mean±S.D.)		
		PA1	PA2	PA3
1	0	0	0	0
2	0.5	37.55±0.54	44.58±0.24	36.54±0.64
3	1	51.47±0.68	56.24±0.28	44.02±0.25
4	2	70.21±1.01	76.88±0.47	58.74±0.84
5	3	86.58±0.99	90.01±0.34	73.46±0.35
6	4	95.47±0.87	97.81±0.98	81.81±0.12
7	5	103.24±0.68	106.33±0.78	89.90±0.27
8	6	119.27±0.52	115.23±0.53	97.41±1.05
9	7	128.29±0.47	120.39±0.35	104.37±1.08
10	8	132.98±0.33	126.67±0.78	111.89±1.06
11	9	137.68±0.24	129.94±0.80	117.76±0.25
12	10	138.03±0.61	133.65±1.02	121.53±0.24

Figure 11
Swelling data of formulation PA1, PA2, PA3

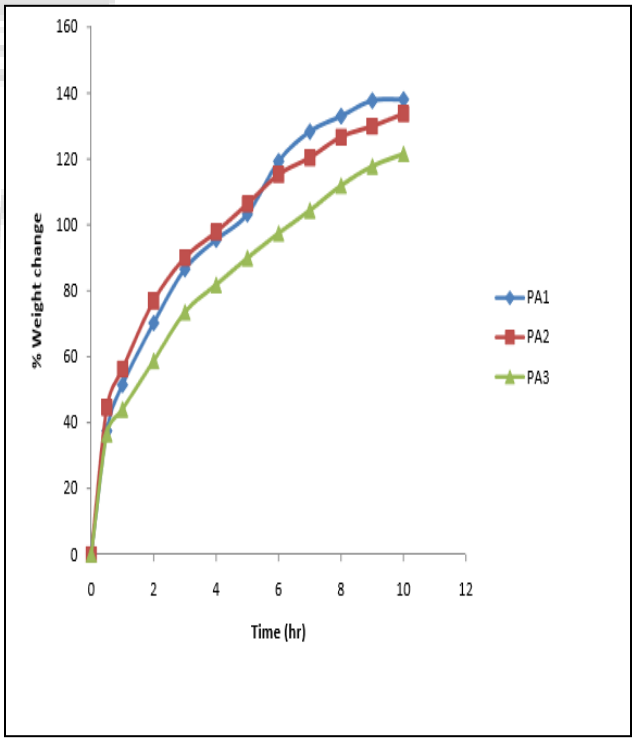
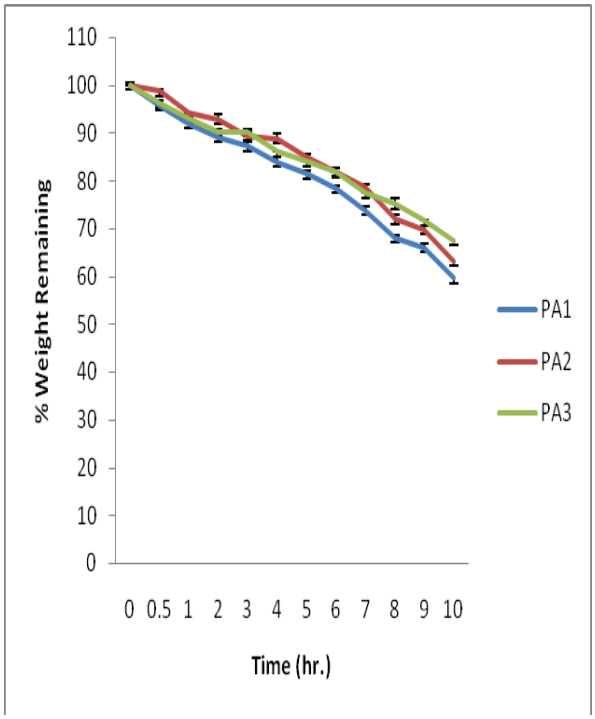


Table 15
Erosion data of formulation PA1, PA2, PA3

S. No.	Time (hr)	% Weight remaining (Mean±S.D.)		
		PA1	PA2	PA3
1	0	100	100	100
2	0.5	95.69±0.68	98.72±0.06	96.30±0.25
3	1	92.04±0.98	94.18±0.25	93.07±0.36
4	2	89.04±0.23	92.96±0.14	90.26±0.54
5	3	87.24±1.02	89.25±1.09	90.25±0.47
6	4	83.98±1.09	88.84±0.99	86.07±0.41
7	5	81.48±0.99	85.06±0.93	84.05±0.21
8	6	78.39±0.67	82.01±0.58	81.71±0.14
9	7	73.83±0.57	78.65±0.83	77.45±0.18
10	8	68.06±0.88	72.02±0.70	75.09±0.28
11	9	66.05±0.45	69.96±0.77	71.66±1.25
12	10	59.65±0.68	63.26±0.79	67.44±0.11

Figure 12
Erosion data of formulation PA1, PA2, PA3



Water uptake (swelling) data were found to be 141.08, 134.85, 123.60, 143.11, 129.46, 119.46, 138.03, 133.65 and 121.53 % weight change for P1, P2, P3, A1, A2, A3, PA1, PA2 and PA3 formulations respectively at the end of 10 hours. Observation indicated that the matrix tablets appeared to swell almost from the beginning, a viscous gel mass was created when they came into contact with the medium, % weight change was found to be increased with decrease in amount of polymers because of complete swelling of polymers in 10 hours. Erosion data were found to be 51.54, 55.66, 62.67, 64.08, 66.71, 72.45, 59.65, 63.27 and 67.44% weight remaining for P1, P2, P3, A1, A2, A3, PA1, PA2 and PA3 formulations respectively at the end of 10^{th} hour. The erosion was found to be increasing with swelling time.

Curve fitting data:

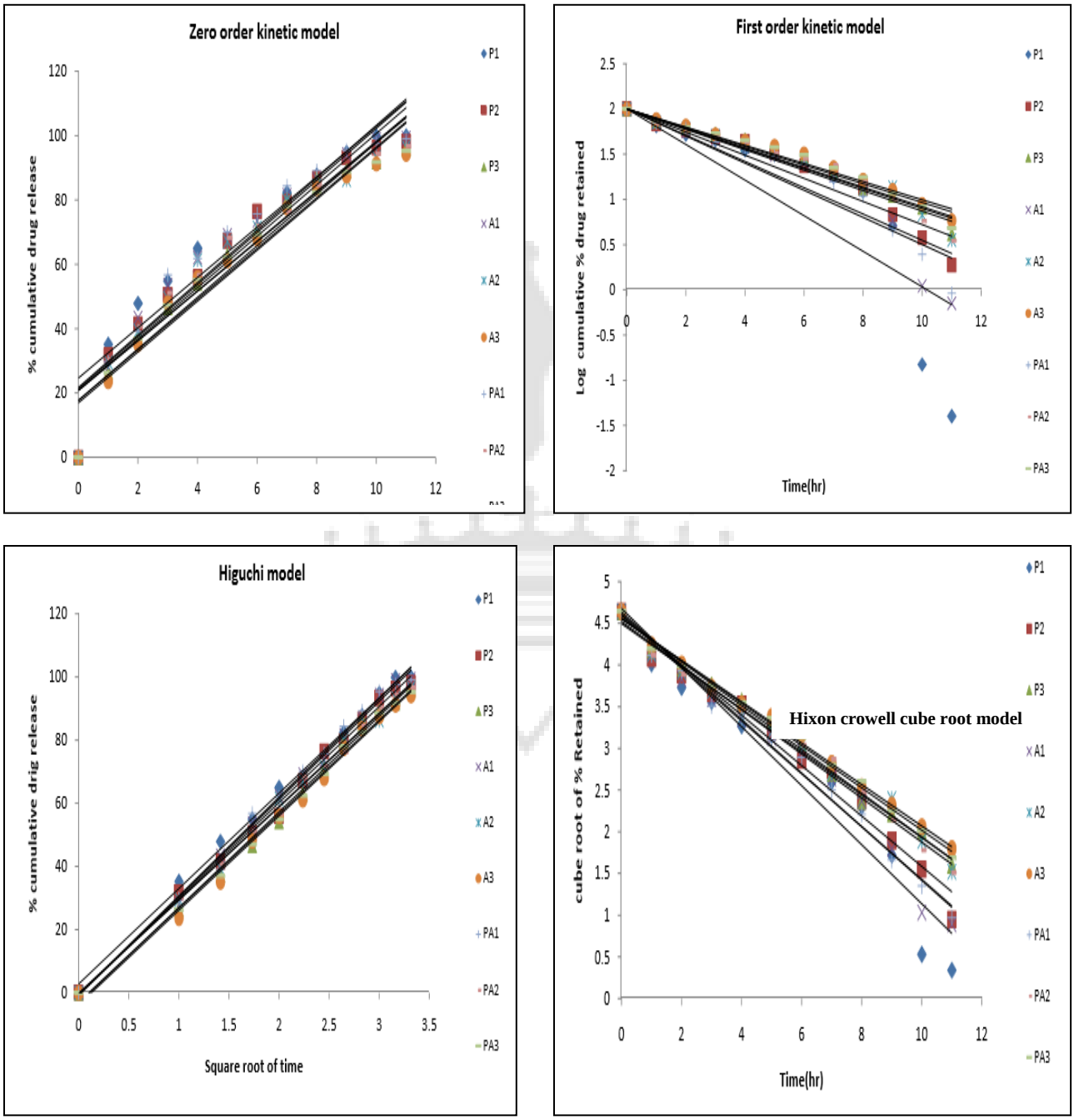
The results of *in vitro* release studies were also fitted into five models to investigate the release as follows:

1. Cumulative % drug release vs. time (Zero order kinetic model).
2. log cum. % drug retained vs. time (First order kinetic model).

3. Higuchi's classical diffusion equation (Higuchi matrix model) in which cumulative % release was plotted against √T (square root of time).

4. Cube root of % retained vs. time (Hixon crowell cube root law).

5. log % cumulative drug release vs. log time (Korsmeyer-Peppas model).



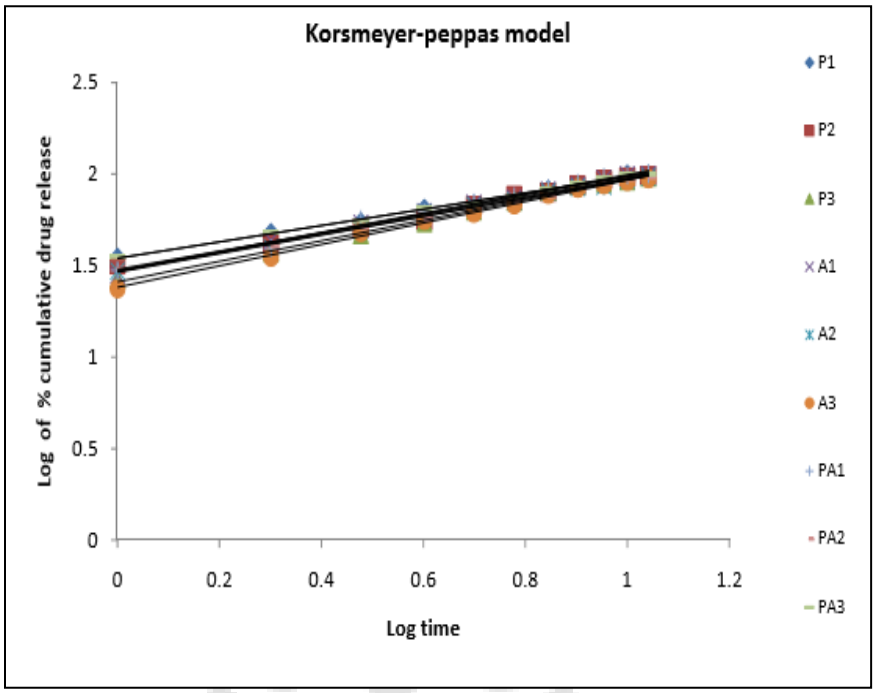


Figure 13. Percentage Cumulative drug release for Zero, First, Higuchi, Hixon Crowell and Korsmeyer Peppas Model

Table 16. Correlation coefficients (r^2) computed from different equations

Formulations	zero order	first order	Higuchi	Hixon crowell	Korsmeyer-Peppas	
	r2	r2	r2	r2	r2	n
P1	0.899	0.676	0.995	0.931	0.995	0.446
P2	0.923	0.916	0.995	0.977	0.990	0.499
P3	0.936	0.961	0.993	0.993	0.995	0.560
A1	0.917	0.830	0.997	0.967	0.995	0.524
A2	0.913	0.945	0.997	0.987	0.994	0.507
A3	0.937	0.972	0.994	0.995	0.995	0.586
PA1	0.909	0.896	0.994	0.988	0.989	0.528
PA2	0.921	0.942	0.997	0.986	0.996	0.498
PA3	0.939	0.960	0.996	0.994	0.995	0.446

r^2 is correlation coefficient calculated by the method of least squares at 95% confidence limit.

Table 5.16 shows data for curve fitting. Based on highest regression values 0.995 the best fit model for P1, P3 and A3 is Korsmeyer-Peppas with n value 0.446, 0.560 and 0.586 respectively suggesting that the drug release was by diffusion follows non-Fickian behavior. The highest r^2 values were 0.995, 0.997, 0.997, 0.994, 0.997 and 0.996 for P2, A1, A2, PA1, PA2 and PA3 formulations respectively for Higuchi matrix indicating that the release is by diffusion. A r^2 value of 0.995 is found for the Higuchi matrix for formulation P1, further supporting that the drug release follows a square root of time relationship. Here formulation P3, A3 and PA3 with r^2 value of 0.993, 0.995 and 0.994 respectively also follows Hixon Crowell's cube root law suggesting that drug release was by erosion.

CONCLUSION

The aim of this study was to formulate and evaluate pectin/alginate based matrix tablets of Metformin HCl. Matrix tablets of different drug polymer ratios were prepared by direct compression method. From the experimental results, it was concluded that:

Matrix tablets of Metformin HCl were prepared by direct compression method using pectin and sodium alginate as a drug release modifier by using different drug polymer ratio. FTIR studies confirmed compatibility between drug-polymer mixture and formulation. DSC studies show crystalline dispersion of Metformin HCl particles into the polymer matrix and the drug is thermally compatible with the polymers. The blends were evaluated for precompression studies and prepared matrix tablets were evaluated for thickness, hardness, weight variation, % friability and drug content.

In vitro drug release showed that the drug release decreases with increase in the amount of polymer added in each formulation. Release studies also showed that the swelling and erosion of matrix tablets influenced the drug release and a bi-phasic release with an initial burst effect due to initial wetting of the polymers cause swelling of outer layer of the tablets. Swelling and erosion data show that the matrix tablets appeared to swell almost from the beginning and erosion was found to be increasing with swelling time. The matrix tablets swelled or eroded while in contact with the aqueous medium and formed a continuous gel layer or underwent combination of swelling and erosion.

Based on mathematical data revealed from models, it was concluded that the best fit model for P1, P3 and A3 is Korsmeyer-Peppas suggesting that the drug release was by diffusion suggesting non-Fickian behavior whereas P2, A1, A2, PA1, PA2 and PA3 follow Higuchi matrix indicating that the release is by diffusion.

As per the release studies, formulation A3 (drug: polymer ratio 2:1) was considered to be the best formulation with 94.16% drug release upto 11 hr, which follows Non-Fickian as well as Hixon crowell's cube root law indicating that the drug release was by diffusion followed by erosion.

SCOPE FOR FURTHER STUDY

Present work was a satisfactory preliminary study in formulation and evaluation of pectin/alginate based matrix tablets of Metformin HCl for sustained drug delivery. Further work can be extended as:

• Improving efficiency of the prepared formulations by carrying out *in-vivo* experiments in animals.

• The further *in-vivo* gamma scintiographic study has to be carried out in human individuals for better prediction of *in-vivo* behavior of the matrix tablets.

• Bioavailability studies can be conducted to assess the relative usefulness of these formulations.

• To establish *in-vitro/in-vivo* correlation to guarantee the efficacy and bioavailability of the formulations.

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