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Design, development and in-vitro evaluation of pinaverium colon targeted tablets

M. Neharika* and Shaik. Harun Rasheed

Department of Pharmaceutical Analysis, Srikrupa institute of Pharmaceutical Sciences, Siddipet - 502277, Telangana, India.

ABSTRACT

In the present research work colon formulation of Pinaverium targeted to colon by using various polymers developed. To achieve pH-independent drug release of Pinaverium, pH modifying agents (buffering agents) were used. Colon targeted tablets were preparedin two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit RLPO and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F6 formulation was found to be optimized as it was retarded the drug release up to 18 hours and showed maximum of 98.45% drug release. It followed first order kinetics mechanism.

Keywords: Pinaverium, Colon targeted drug delivery system, Ethyl cellulose, Eudragit RLPO, Eudragit S 100

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Corresponding Author

Name: M. Neharika
Email: niharikamamilla047@gmail.com

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INTRODUCTION

Now a days a novel oral colon-specific drug delivery system (CDDS) has been developed as one of the site-specific drug delivery systems[1]. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration[2]. First as for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation etc., the optimal drug delivery system, such as CDDS, should selectively deliver drug to the colon, but not to the upper GI tract[3]. Second, the colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon. Finally, CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis. Pinaverium is a spasmolytic agent used for functional gastrointestinal disorders[4]. It is a quaternary ammonium compound that acts as an atypical calcium antagonist to restore normal bowel function. It is shown to relieve GI spasm and pain, transit disturbances and other symptoms related to motility disorders and may be considered as effective first-line therapy for patients with irritable bowel syndrome (IBS)[5]. Pinaverium bromide is the common ingredient in formulations, mostly as oral tablets.

MATERIALS AND METHODS

Pinaverium was obtained as gift sample from Natco LABS, Hyderabad. Ethyl Cellulose was obtained from Signet Chemical Corporation, Mumbai, India. Eudragit RLPO, Eudragit L-100 Cross carmellose sodium Magnesium Stearate and Microcrystalline cellulose was purchased from Merck Specialties Pvt Ltd, Mumbai, India.

Analytical method development

a) Determination of absorption maxima: A solution of containing the concentration 10 µg/ ml was prepared in 0.1N Hcl, 7.4 pH & phosphate buffer 6.8 pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) Preparation calibration curve: 10mg of drug was accurately weighed and dissolved in 10ml of 0.1N Hcl, 7.4 pH, and 6.8 pH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4, 6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N Hcl, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 270nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Table 1: Observations for graph of Pinaverium in 7.4 pH Simulated Intestinal Fluid (nm)

S.No	Conc.(mg/l)	Abs		
		7.4 pH	0.1N Hcl	6.8 pH
1	0	0	0	0.148
2	2	0.129	0.138	0.275
3	4	0.204	0.256	0.379
4	6	0.284	0.376	0.481
5	8	0.372	0.461	0.621
6	10	0.566	0.582	0.859
7	12	0.625	0.824	0.148

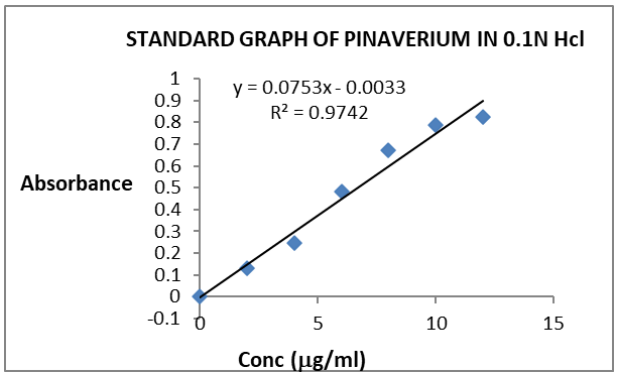

Figure 1: Standard graph of Pinaverium in 0.1N Hcl

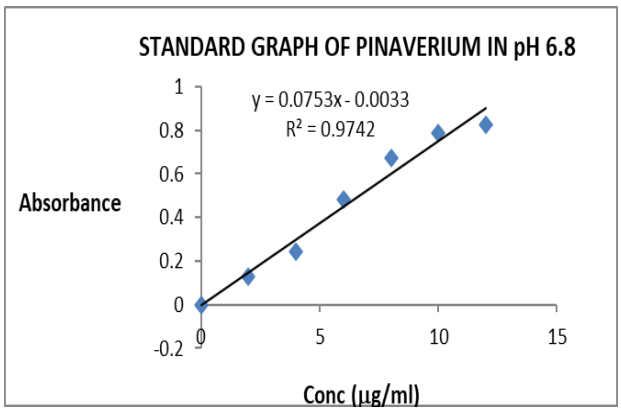

Figure 2: Standard graph of Pinaverium in 6.8 pH

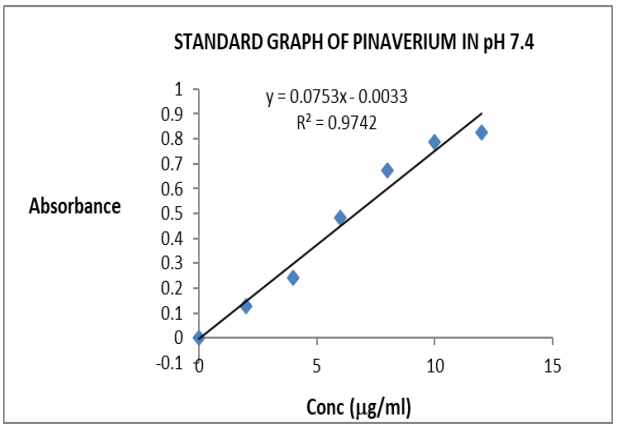

Figure 3: Standard graph of Pinaverium in 7.4 pH

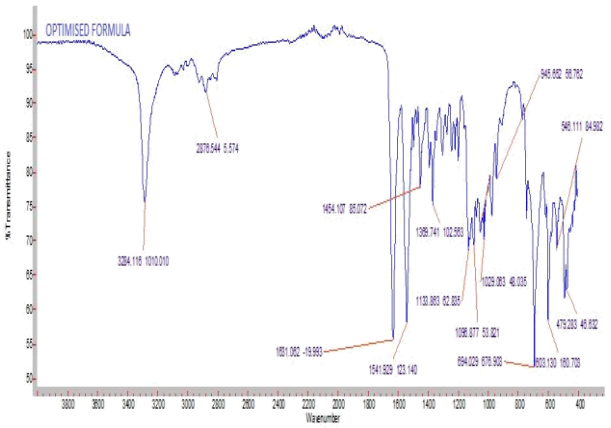

Figure 4: FT-IR spectrum of pure drug

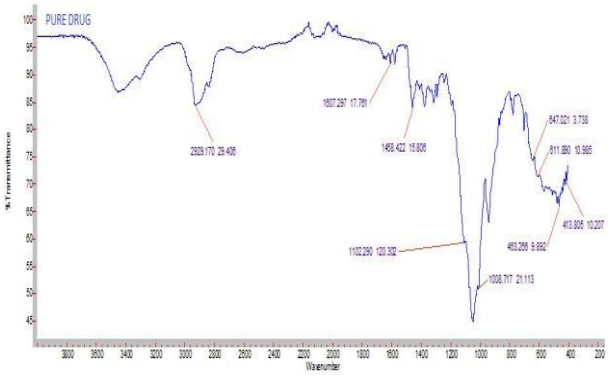

Figure 5: FTIR spectrum of optimized formulation

Drug – excipient compatibility studies

Fourier Transform Infrared (FTIR) Spectroscopy: The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations

Table 2: Composition of coating layer

S.No	Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ethyl cellulose (mg)	50	100	-	-	-	-	50	-	50
2	Eudragit RLPO (mg)	-	-	50	100	-	-	50	50	-
3	Eudragit L 100 (mg)	-	-	-	-	50	100	-	50	50
4	Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3
5	Talc (mg)	3	3	3	3	3	3	3	3	3
6	MCC pH 102 (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Total weight	280	280	280	280	280	280	280	280	280

Table 3: Pre-formulation parameters of Core Powder

Formulation code	Angle of Re-pose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio
F1	26.01	0.55	0.645	14.72	0.85
F2	24.8	0.57	0.66	13.63	0.86
F3	26.05	0.53	0.606	14.19	0.838
F4	24.19	0.531	0.613	13.37	0.866
F5	26.24	0.549	0.641	14.35	0.856
F6	23.25	0.564	0.666	15.31	0.854
F7	27.08	0.581	0.671	13.41	0.865
F8	25.12	0.567	0.654	13.12	0.845
F9	25.45	0.571	0.689	13.28	0.855

Table 4: In-vitro quality control parameters for compression coated tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug Content (%)
F1	402.5	4.5	0.52	4.8	99.76
F2	405.4	4.2	0.54	4.9	99.45
F3	398.6	4.4	0.51	4.9	99.34
F4	410.6	4.5	0.55	4.9	99.87
F5	409.4	4.4	0.56	4.7	99.14
F6	410.7	4.2	0.45	4.5	98.56
F7	402.3	4.1	0.51	4.4	98.42
F8	401.2	4.3	0.49	4.7	99.65
F9	398.3	4.5	0.55	4.6	99.12

Table 5: In-vitro Drug Release profile for coated formulations (F1-F9)

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	3.77	9.14	5.12	8.23	2.71	5.46	4.11	3.11	5.54
1	10.51	16.76	12.45	17.55	11.51	17.54	12.35	7.15	12.17
2	18.4	25.77	17.47	22.42	19.4	24.72	19.42	14.21	24.58
3	24.15	29.42	23.42	28.11	23.17	31.76	25.12	27.54	33.19
4	32.13	34.64	29.18	36.67	31.18	37.62	32.15	35.45	39.79
5	37.91	41.32	36.71	48.71	36.91	46.87	36.36	45.21	48.69
6	42.92	49.12	41.78	56.86	42.92	49.09	40.54	53.77	52.75
7	48.18	52.77	48.89	59.49	49.16	53.72	46.39	56.34	54.38
8	54.32	56.85	52.22	62.46	53.32	56.73	51.21	58.73	56.54
9	59.93	59.32	54.42	65.19	58.93	61.41	57.54	61.69	58.28
10	63.82	61.98	58.34	69.42	62.85	63.32	62.36	63.54	62.19
11	65.77	63.27	60.42	71.12	64.71	68.13	64.28	65.15	64.14
12	68.22	65.72	62.47	72.41	66.34	78.28	68.03	66.49	66.68
13	69.35	69.35	64.28	73.89	68.98	82.54	72.35	68.45	69.84
14	71.23	72.65	66.38	75.67	71.26	84.32	74.85	69.87	72.36
15	73.63	74.28	69.45	77.98	73.45	87.98	77.21	72.45	74.38
16	75.39	76.37	72.56	79.82	75.28	92.98	79.45	74.36	77.45
17	77.28	78.36	75.23	81.25	79.32	95.64	82.37	76.29	78.52
18	79.12	82.21	77.87	83.65	84.36	98.45	85.87	79.34	83.28

and process variables involved in mixing and all these can affect the characteristics of blends produced[6].

Angle of repose: The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the

surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface.

The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\text{Tan } \theta = h / r$$

Where; Tan θ = Angle of repose, h = Height of the cone, r = Radius of the cone base

Bulk density: Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume Vo was read. The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / Vo$$

M = weight of sample, Vo = apparent volume of powder

Tapped density: After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density, Tap = Tapped Density

Composition of core tablet[7]: Total weight of core tablet was fixed as 7.5 mg. The tablets are prepared by using 6mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets[8]: The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials. The composition of coating layer is given in below table.

Compression coating layer was divided into two equal portions i.e., 140mg of each quantity .Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 10mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm^2.Then the prepared compression coated tablets are evaluated for various post compression parameters as per standard specifications[9].

Evaluation of post compression parameters for prepared tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content[10].

Weight variation test: To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W] \times 100$$

Table 6: Release Rate Kinetics to Dissolution Data

Cumulative (%) release Q	Time (t)	Root (t)	Log (%) Release	Log (t)	Log (%) Remain
0	0	0			2.000
5.46	0.5	0.707	0.737	-0.301	1.976
17.54	1	1.000	1.244	0.000	1.916
24.72	2	1.414	1.393	0.301	1.877
31.76	3	1.732	1.502	0.477	1.834
37.62	4	2.000	1.575	0.602	1.795
46.87	5	2.236	1.671	0.699	1.725
49.09	6	2.449	1.691	0.778	1.707
53.72	7	2.646	1.730	0.845	1.665
56.73	8	2.828	1.754	0.903	1.636
61.41	9	3.000	1.788	0.954	1.586
63.32	10	3.162	1.802	1.000	1.564
68.13	11	3.317	1.833	1.041	1.503
78.28	12	3.464	1.894	1.079	1.337
82.54	13	3.606	1.917	1.114	1.242
84.32	14	3.742	1.926	1.146	1.195
87.98	15	3.873	1.944	1.176	1.080
92.98	16	4.000	1.968	1.204	0.846
95.64	17	4.123	1.981	1.230	0.639
98.45	18	4.243	1.993	1.255	0.190

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content: Ten tablets were finely powdered quantities of the powder equivalent

to one tablet weight of Pinaverium were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

Drug release studies of Compression coated Pinaverium tablets: The release of Pinaverium from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used up to 12 hours to mimic colonic pH conditions and finally the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release up to 18 hours. Drug release was measured from compression coated Pinaverium tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batches. The results were given with deviation.

Application of Release Rate Kinetics To Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmayer-Peppa's release model.

Zero order release rate kinetics: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = Kot$$

Where, 'F' is the drug release at time't', and 'Ko' is the zero order release rate constant.

The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\, t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

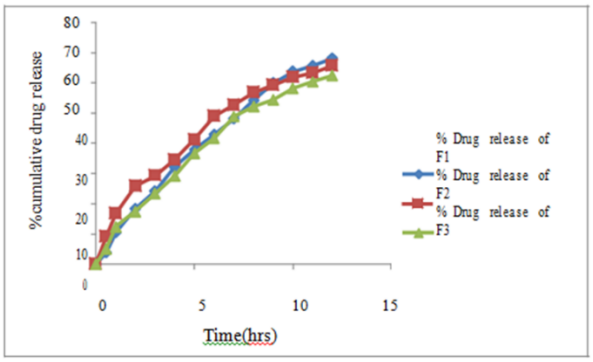

Figure 6: Dissolution of formulations F1-F3

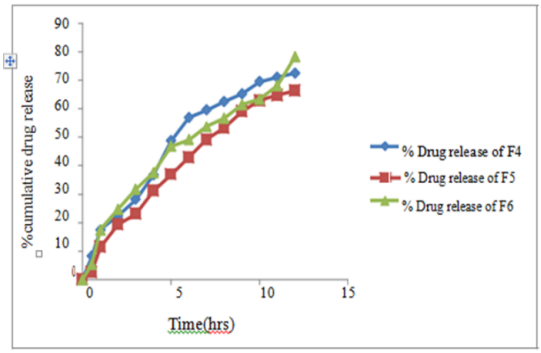

Figure 7: Dissolution of formulations F4-F6

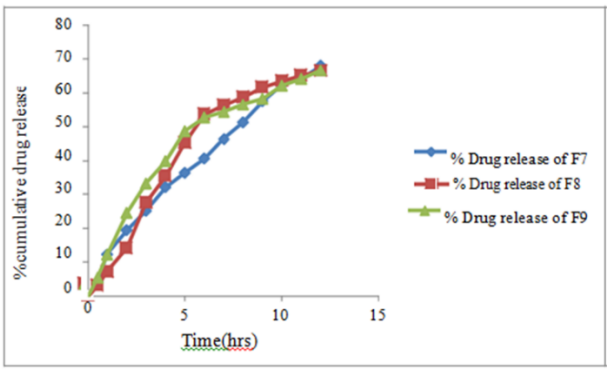

Figure 8: Dissolution of formulations F7-F9

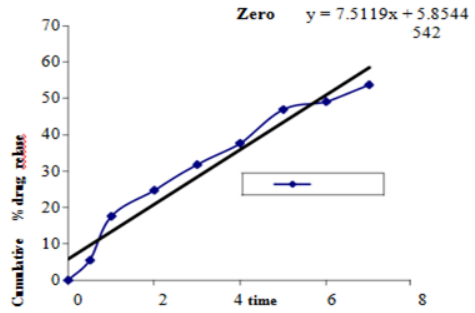

Figure 9: Zero order release kinetics graph of F6

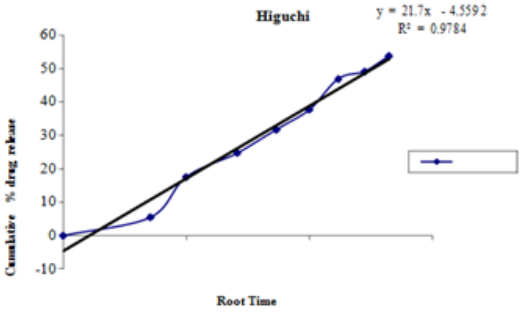

Figure 10: Higuchi release kinetics graph of F6

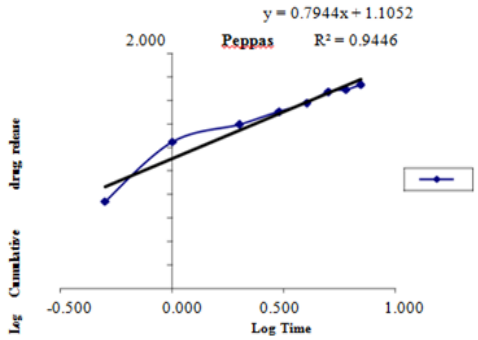

Figure 11: Korsmayer peppa's graph of F6

Korsmayer and Peppa's release model: The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmayer- Peppa's equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$Mt/ M\infty = K t^n$$

Where, Mt/ M∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (Mt/ M∞) versus log (time) is linear.

Hixson-Crowell release model: $(100\text{-}Qt)^{1/3} = 100^{1/3}\text{- KHC.t}$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

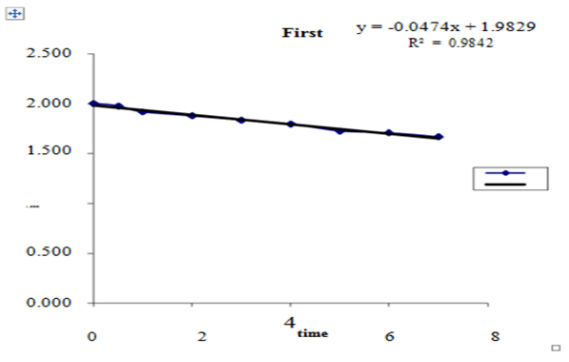

Figure 12: First order release kinetics graph of F6

RESULTS AND DISCUSSION

Analytical Method: Graphs of Pinaverium was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4)

Pinaverium blend was subjected to various pre-formulation parameters The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Tables 7.4, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Quality Control Parameters For compression coated tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 300 mg.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmayer - Peppa's release model.

CONCLUSION

In the present research work of Pinaverium targeted to colon by using various polymers developed. To achieve pH-independent drug release of Pinaverium, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation parameters. The tablets were passed all the tests. Among all the formulations F6 formulation was found to be optimized as it was retarded the drug release up to 18 hours and showed maximum of 98.45% drug release. It followed first order kinetics mechanism with followed by non-fickian diffusion. The results clearly stated that the Pinaverium colon release tablets can sustain the release of the drug with a maximum release and it can be concluded that Pinaverium tablets were successfully prepared for colon targeting.

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