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FORMULATION AND EVALUATION OF PINAVERIUM COLON TABLETS

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Abstract:

Pinaverium bromide (INN) is a medication used for functional gastrointestinal disorders. It belongs to a drug group called antispasmodics and acts as a calcium channel blocker in helping to restore the normal contraction process of the bowel. It is most effective when taken for a full course of treatment and is not designed for immediate symptom relief or sporadic, intermittent use. In the present research work sustained release matrix 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 prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit RLPO and L100 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 F5 formulation was found to be optimized as it was retarded the drug release up to 18 hours and showed maximum of 98.19% drug release. It followed higuchi kinetics mechanism.

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

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INTRODUCTION:

One of the site-specific drug delivery systems that has been developed recently is the oral colon-specific drug delivery system (CDDS). After oral administration, the medication is rapidly released in the colon but scarcely released in the upper gastrointestinal (GI) tract because to this delivery system's combination of one or more controlled release mechanisms2. In order to treat localized colonic disorders, such as ulcerative colitis, Crohn's disease, constipation, etc., the best drug delivery system, like CDDS, should transfer the medication just to the colon and not to the upper gastrointestinal tract. Second, due to its relatively low proteolytic enzyme activity and lengthy transit time, the colon is known as the best location for protein and polypeptide bsorption following oral administration. Last but not least, CDDS might be helpful in treating conditions including nocturnal asthma, angina, and rheumatoid arthritis that have circadian rhythms and peak symptoms in the early morning when a therapeutic delay in absorption is desired. A spasmolytic medication called pinaverium is used to treat functional gastrointestinal disorders. This quaternary ammonium molecule restores normal bowel function by acting as an atypical calcium antagonist. It may be a good first-line treatment for people with irritable bowel syndrome (IBS) because it has been demonstrated to reduce GI pain and spasms, transit disruptions, and other symptoms associated with motility abnormalities. The most often used constituent in formulations is pinaverium bromide, which is often found in oral tablets.

MATERIALS AND METHODS:

A free sample of pinaverium was acquired from Natco LABS in Hyderabad. We purchased ethyl cellulose from Signet Chemical Corporation in Mumbai. Eudragit RLPO, Eudragit L-100 Cross carmellose sodium magnesium stearate, and microcrystalline cellulose obtained from Merck Specialties Pvt Ltd.

Preformulation parameters of coating material

Table1: Pre-formulation parameters of compression blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped densit (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.25	0.56	0.65	15.42	0.86
F2	24.45	0.58	0.67	14.73	0.87
F3	27.05	0.54	0.61	15.89	0.84
F4	25.79	0.55	0.62	14.12	0.87
F5	23.75	0.53	0.65	15.78	0.86
F6	24.45	0.57	0.68	16.51	0.88
F7	26.08	0.59	0.64	13.81	0.87
F8	25.82	0.55	0.66	15.52	0.85
F9	24.75	0.54	0.67	14.18	0.83

Pinaverium blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.53 to 0.59 and 0.61 to 0.68 respectively. According to Tables 4.4, the results of angle of repose and compressibility index (%) ranged from 23.25 to 27.08 and 13.81 to 16.51 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 core tablets

Table: 2. Invitro quality control parameters for compression coated tablets

Quality Control parameters	Core material
Weight variation(mg)	119
Hardness(kg/cm2)	2.6
Friability (%loss)	0.52
Thickness (mm)	2.4
Drug content (%)	98.24
Disintegration Time(mins)	1.42

4.5.1. Quality Control Parameters For compression coted 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.

Table: 3. In-vitro quality control parameters for compression coated tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	303.6	4.6	0.53	4.9	99.45
F2	306.5	4.3	0.55	4.7	98.34
F3	300.7	4.5	0.52	4.8	98.87
F4	304.8	4.3	0.56	4.6	98.14
F5	310.5	4.5	0.57	4.8	98.56
F6	308.6	4.3	0.46	4.4	99.42
F7	304.2	4.2	0.52	4.5	99.65
F8	302.1	4.4	0.50	4.8	98.12
F9	299.4	4.1	0.56	4.7	98.57

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

The compression coated tablets containing 100mg of Pinaverium were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of Pinaverium from compression 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, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 6.8) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 7.4) was used upto 18 hours to mimic colonic pH conditions.

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 258 nm , 258 nm and 258 nm respectively. All dissolution runs were performed for six batches.

Table 4: *In-vitro* Drug Release profile for coated formulations (F1-F9)

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	6.22	6.78	7.02	4.89	7.62	5.12	8.38	5.36	4.72
1	11.67	11.35	15.98	12.65	16.75	11.45	14.15	11.57	8.58
2	21.45	17.54	22.56	19.16	21.52	22.65	22.10	18.81	14.39
3	33.46	24.24	35.67	26.57	33.16	30.78	30.74	20.98	19.45
4	38.65	33.35	40.62	32.48	40.93	36.72	33.23	25.46	24.78
5	49.72	40.36	49.86	38.47	43.78	40.11	42.52	29.40	28.37
6	51.71	42.82	53.43	43.53	48.83	45.89	47.82	36.34	36.75
7	57.08	46.75	56.98	45.12	56.45	48.36	55.52	42.56	44.23
8	61.62	53.92	59.78	50.21	57.76	52.48	61.29	48.81	48.38
9	67.32	58.12	64.92	57.54	62.47	57.29	63.13	54.18	52.34
10	69.98	64.42	68.43	63.27	66.73	59.23	67.80	59.98	56.34
11	70.76	70.26	72.25	67.46	70.18	69.75	69.63	65.35	58.31
12	74.25	73.12	75.42	80.75	73.25	74.56	71.95	70.34	64.36
13	78.32	77.52	78.38	83.63	79.36	76.65	75.44	73.43	70.63
14	82.51	82.31	82.13	85.75	86.79	79.42	78.75	80.83	74.71
15	84.54	86.67	84.34	88.17	91.27	83.56	81.94	84.98	77.34
16	87.45	88.91	86.76	90.65	93.69	86.19	85.09	86.52	80.43
17	89.59	89.31	89.92	92.32	96.45	88.35	88.26	89.62	83.27
18	91.82	90.89	93.42	91.85	98.19	91.12	90.83	90.73	86.86

From the dissolution values it was evident that the formulations F4 shown maximum drug release of 98.73 in 18hours hence it was considered as the optimized formulation.

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 Korsmeyer-Peppas release model.

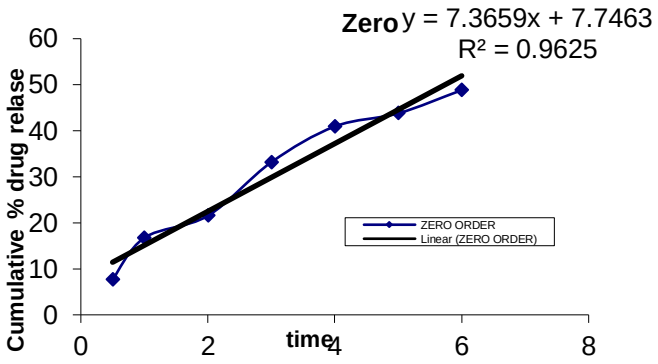

Figure 1 : Zero order release kinetics graph

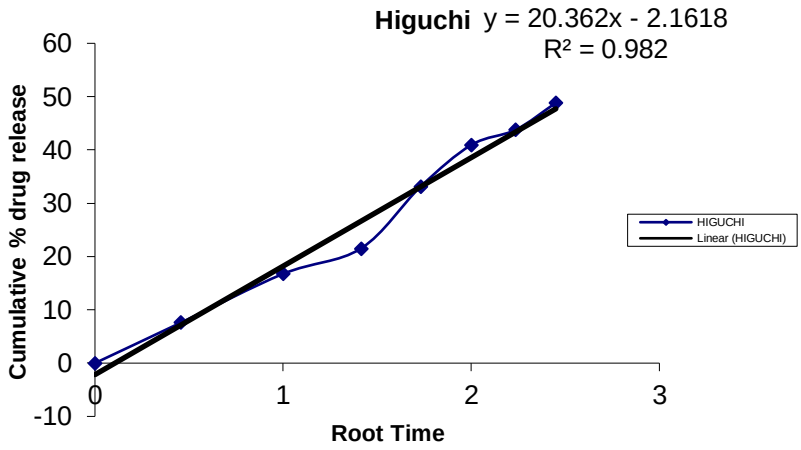

Figure 2: Higuchi release kinetics graph

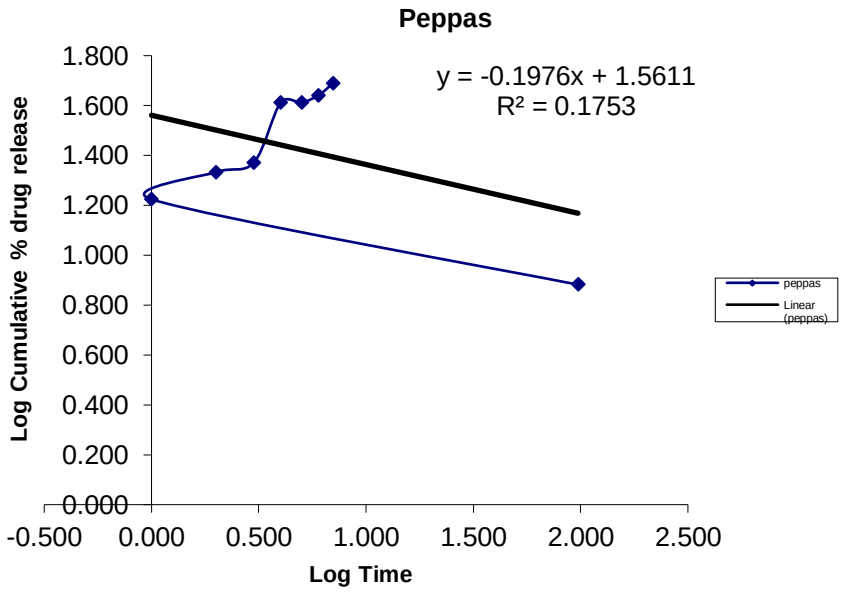

Figure 3: Kars mayer peppas graph

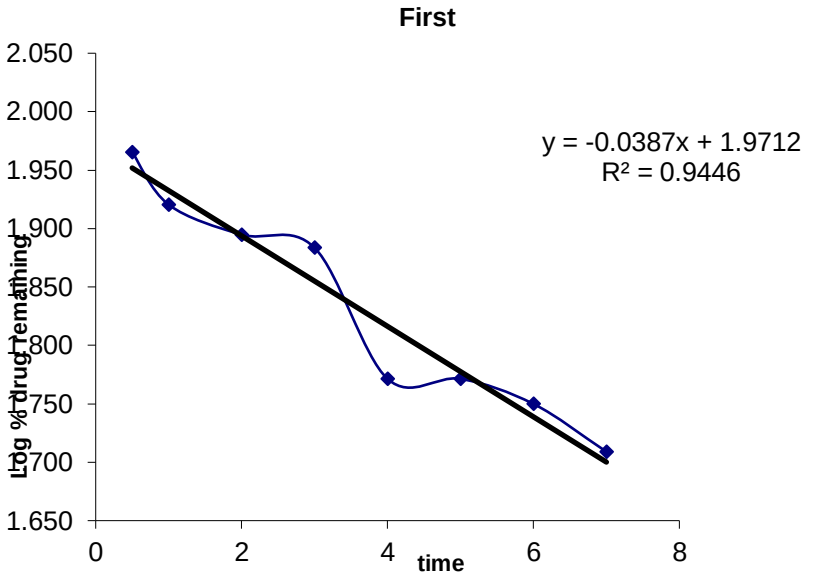

Figure 4.: First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed peppas release kinetics.

CONCLUSION:

In the present research work sustained release matrix 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 prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit RLPO and L100 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 F5 formulation was found to be optimized as it was retarded the drug release up to 18 hours and showed maximum of 98.19% drug release. It followed higuchi kinetics mechanism.

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