FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF ITOPRIDE HYDROCHLORIDE

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ABSTRACT

The objective of this research work was to develop sustained release tablets of Itopride HCl using different hydrophilic polymers like HPMC K4M, HPMC K15M, Carbopol 971P, Metolose 60SH-50, Guar gum, Xanthan gum by direct compression method. Various amounts of combination of polymers in 1:1 ratio were used in the twenty four proposed formulations (F-1 to F-24) for the study of release rate retardant effect at 15 %, 25 % and 35 % of total weight of tablet matrix respectively. Then the tablets were evaluated in terms of their physical parameters (weight variation, hardness, friability and thickness), drug content and *In-vitro* release studies. All the formulations showed compliance with pharmacopoeial standards. The *In-vitro* dissolution study were conducted using USP dissolution apparatus type II (paddle method) in 900 ml 0.1 N HCl for first 2 h and remaining 22 h performed in 6.8 pH phosphate buffer at 50 rpm for a total period of 24 h. Based on the dissolution data comparison with innovator, formulation F-8 was found as the best formulation. The drug release of formulation F-8 followed First Order kinetic model and the mechanism was found to be non-Fickian / anomalous according to Korsmeyer-Peppas equation.

Keywords: Itopride Hydrochloride, Direct Compression, Carbopol 971P, Sustained Release.

INTRODUCTION

In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages. Sustained release tablet formulations are designed to slowly release a drug in the body over an extended period of time. Sustained formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects¹. Itopride Hydrochloride is an oral prokinetic agent used in the treatment of gastric motility disorder. It is benzamide derivative, absorbed from gastrointestinal tract. Itopride Hydrochloride activates the gastrointestinal motility through synergism of its dopamine D₂ receptor antagonistic action and its acetylcholinesterase-inhibitory action. In addition to these actions, Itopride has an antiemetic action, which is based on its dopamine D₂-receptor antagonistic action. The short biological half-life (6 h), 60 % bioavailability and dosage frequency more than once a day (50 mg t.i.d.) make the Itopride Hydrochloride an ideal candidate for the controlled drug delivery systems. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Itopride Hydrochloride is desirable. The most commonly used method of modulating the drug release is to include it in a matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network^{2,3}.

MATERIALS AND METHODS:

Materials

Itopride hydrochloride was received as a gift sample from Qualitech pharma. HPMCK4M, HPMCK15M, Carbopol971P, Xanthan gum, Metolose 60SH-50, Guar gum,

Micro crystalline cellulose, Magnesium stearate, Aerosil, obtained from Richer Pharmaceuticals.

Methods

Drug Excipient Compatibility Studies

Compatibility study was carried for pure Itopride Hydrochloride and combination of Itopride Hydrochloride with excipients. Fourier transfer infra red (FTIR) spectroscopic (shimadzu, Japan) studies were carried out by approximately diluting the sample with dried potassium bromide (1:100) and acquiring infrared (IR) spectrum in the range of 400 to 4000 cm⁻¹.

Formulation of Sustained release matrix tablets Itopride Hydrochloride by Direct compression

Various formulation batches of Itopride Hydrochloride Sustained release tablets were prepared using different polymers at 15 %, 25 %, 35 % Concentration of total weight of tablet matrix respectively. All ingredients except magnesium stearate were blended in glass mortar uniformly. Then pass the mixture through sieve # 60. Add magnesium stearate to the above mixture and pass through sieve # 60 and mix for 10-15 minutes; finally compressed in concave shaped circular punches 8.5 mm (Cadmach 16 station).

Evaluation Parameters

Evaluation of powder blend

Angle of repose

Static angle of repose was determined according to the fixed funnel method; where by accurately weighed powder (3 g) were carefully poured through the funnel with its tip at 2 cm height (H), until the apex of the conical heap so formed just reached the tip of the funnel⁴. The mean diameter 2R of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation.

$$\tan(\theta) = H/R$$

Bulk density and tapped density

Both poured bulk and tapped bulk densities were determined, where by a quantity (3 g) of powder blend from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in the volume was noted.

Carr's Compressibility Index and Hausner's ratio

The compressibility of the powder was determined by carr's compressibility index (CI). The Hausner's ratio (HR) is number that is correlated to the flow ability of powder.

CI = ((TD-BD)/TD)*100 where TD = tapped density and BD = bulk density.
HR = (100/100-CI)

Evaluation of tablets

The prepared sustained release tablets were evaluated for hardness, thickness, friability, weight variation test and drug content. Hardness of tablets was tested using Monsanto hardness tester (Serve well, Bangalore, India). Friability of the tablets was determined in a Roche Friabilator (Electrolab, Mumbai, India). The thickness of tablets was measured by vernier calipers. Weight variation test was performed according to official method. Drug content for Itopride Hydrochloride was carried out by measuring the absorbance of samples at 263 nm using Lab India UV-2400 PC spectrophotometer Mumbai, India and comparing the content from a calibration curve of Itopride Hydrochloride⁵.

In-vitro drug release study

Release of the prepared tablets was determined up to 24 h using USP XXIV (Type-II) dissolution rate test apparatus (Electro lab Mumbai). 900 ml of 0.1N HCl was used as dissolution medium for first two hours then using 6.8phosphate buffer for up to 24 h. The rotation of paddle was fixed at 50 rpm and the temperature of $37 \pm 0.5^\circ\text{C}$ was maintained throughout the experiment. Samples of 10 ml were withdrawn at 1, 2, 4, 6, 8, 12, 16, 20, 24 h time intervals and were placed with same volume of fresh dissolution media after each with drawn. The samples were analyzed spectrophotometrically for drug content on UV/Visible spectrophotometer-2400PC Lab India Mumbai at 263 nm.^{6,7}

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies reveals that the pure drug Itopride Hydrochloride and the solid admixture of drug and various ingredients used in the preparation of sustained release tablets were characterized by FTIR spectroscopy to know the compatibility. There was no significant difference or the characteristic peak of pure drug was unchanged in spectrum of optimized formulation (F8). Micromeritic properties like angle of repose value of $27.69-36.28^\circ$, Carr's index value of 12.72-16.16 and Hausner's ratio 1.15-1.18 indicating flow property excellent to fair. Hence powder mixture was found suitable for direct compression method. Post compression parameters like hardness of the tablet were acceptable and uniform from batch to batch variation, which was found to be 5.5-7.5 kp. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of $\pm 5\%$ of the tablet weight. Friability values were found to be less than 1 % in all the formulations F1 – F24 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

Table 1: Composition of the Formulations (per each tablet in mg)

Formulation code	Drug	Mcc	PvpK30	Carbopol 971P	Hpmck4M	Hpmc kl5M	Metolose 60SH50	Xanthan gum	Guar Gum	Aerosil	Mag. stearate	Total (mg/ tab)
F1	150	160	20	30	30	-	-	-	-	5	5	400
F2	150	120	20	50	50	-	-	-	-	5	5	400
F3	150	80	20	70	70	-	-	-	-	5	5	400
F4	150	160	20	-	-	-	30	-	30	5	5	400
F5	150	120	20	-	-	-	50	-	50	5	5	400
F6	150	80	20	-	-	-	70	-	70	5	5	400
F7	150	160	20	30	-	30	-	-	-	5	5	400
F8	150	120	20	50	-	50	-	-	-	5	5	400
F9	150	80	20	70	-	70	-	-	-	5	5	400
F10	150	160	20	-	-	-	30	30	-	5	5	400
F11	150	120	20	-	-	-	50	50	-	5	5	400
F12	150	80	20	-	-	-	70	70	-	5	5	400
F13	150	160	20	30	-	-	-	-	30	5	5	400
F14	150	120	20	50	-	-	-	-	50	5	5	400
F15	150	80	20	70	-	-	-	-	70	5	5	400
F16	150	160	20	-	-	-	-	30	30	5	5	400
F17	150	120	20	-	-	-	-	50	50	5	5	400
F18	150	80	20	-	-	-	-	70	70	5	5	400
F19	150	160	20	30	-	-	30	-	-	5	5	400
F20	150	120	20	50	-	-	50	-	-	5	5	400
F21	150	80	20	70	-	-	70	-	-	5	5	400
F22	150	160	20	30	-	-	-	30	-	5	5	400
F23	150	120	20	50	-	-	-	50	-	5	5	400
F24	150	80	20	70	-	-	-	70	-	5	5	400

Table 2: Pre Compression parameters

Formulation code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	30.85 ± 1.06	0.41 ± 0.26	0.49 ± 0.82	15.35 ± 0.78	1.18 ± 0.84
F2	29.26 ± 0.74	0.42 ± 0.47	0.49 ± 0.74	14.28 ± 0.42	1.16 ± 0.72
F3	27.69 ± 0.62	0.44 ± 0.12	0.51 ± 0.26	12.89 ± 0.19	1.14 ± 0.26
F4	36.84 ± 1.14	0.43 ± 0.63	0.52 ± 0.35	16.09 ± 0.36	1.19 ± 0.53
F5	32.18 ± 1.02	0.43 ± 0.54	0.50 ± 0.26	14.82 ± 0.64	1.17 ± 0.82
F6	30.28 ± 0.83	0.45 ± 0.46	0.52 ± 0.12	14.12 ± 0.27	1.16 ± 0.29
F7	30.11 ± 0.54	0.42 ± 0.38	0.49 ± 0.46	14.08 ± 0.49	1.16 ± 0.34
F8	28.06 ± 0.32	0.44 ± 0.21	0.51 ± 0.22	12.72 ± 0.26	1.14 ± 0.65
F9	27.13 ± 0.15	0.46 ± 0.18	0.53 ± 0.12	12.64 ± 0.15	1.14 ± 0.29
F10	36.12 ± 1.28	0.42 ± 0.49	0.49 ± 0.28	15.32 ± 0.61	1.18 ± 0.41
F11	32.14 ± 1.06	0.41 ± 0.2	0.48 ± 0.23	14.34 ± 0.84	1.16 ± 0.87
F12	29.95 ± 0.87	0.40 ± 0.16	0.47 ± 0.11	14.6 ± 0.52	1.17 ± 0.26
F13	36.28 ± 1.13	0.41 ± 0.21	0.49 ± 0.79	16.16 ± 0.35	1.19 ± 0.39
F14	31.17 ± 0.96	0.44 ± 0.39	0.52 ± 0.58	15.26 ± 0.61	1.18 ± 0.41
F15	29.28 ± 0.72	0.44 ± 0.17	0.51 ± 0.24	14.39 ± 0.42	1.16 ± 0.69
F16	32.16 ± 1.18	0.41 ± 0.28	0.49 ± 0.29	15.10 ± 0.19	1.17 ± 0.18
F17	30.12 ± 0.91	0.44 ± 0.32	0.510 ± 0.37	13.3 ± 0.36	1.15 ± 0.84
F18	28.25 ± 0.21	0.44 ± 0.24	0.51 ± 0.18	12.98 ± 0.51	1.14 ± 0.40
F19	33.52 ± 1.11	0.43 ± 0.29	0.50 ± 0.26	13.6 ± 0.35	1.15 ± 0.26
F20	32.60 ± 1.42	0.40 ± 0.27	0.47 ± 0.89	14.55 ± 0.82	1.17 ± 0.62
F21	29.32 ± 0.64	0.41 ± 0.45	0.47 ± 0.73	14.22 ± 0.39	1.16 ± 0.31
F22	30.97 ± 0.82	0.45 ± 0.19	0.52 ± 0.54	13.76 ± 0.26	1.15 ± 0.18
F23	29.82 ± 0.39	0.40 ± 0.24	0.473 ± 0.42	14.16 ± 0.21	1.16 ± 0.24
F24	28.21 ± 0.24	0.44 ± 0.16	0.515 ± 0.18	12.81 ± 0.13	1.14 ± 0.12

Table 3: Post compression parameters

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Drug content (%)
F-1	398 ± 1.96	4.87 ± 0.6	5.5-7.5	0.52 ± 0.76	99.3 ± 0.59
F-2	400 ± 1.82	4.88 ± 0.3	5.5-7.5	0.47 ± 0.48	99.5 ± 0.16
F-3	400 ± 0.54	4.89 ± 0.3	5.5-7.5	0.39 ± 0.39	99.8 ± 1.05
F-4	399 ± 0.15	4.89 ± 0.4	5.5-7.5	0.46 ± 0.61	100.4 ± 0.15
F-5	399 ± 0.65	4.80 ± 0.2	5.5-7.5	0.34 ± 0.52	101.0 ± 0.6
F-6	400 ± 0.89	4.86 ± 0.4	5.5-7.5	0.25 ± 0.43	99.4 ± 0.84
F-7	399 ± 1.04	4.88 ± 0.5	5.5-7.5	0.66 ± 0.82	98.4 ± 0.42
F-8	400 ± 0.28	4.89 ± 0.2	5.5-7.5	0.38 ± 0.18	99.7 ± 0.68
F-9	400 ± 0.76	4.89 ± 0.7	5.5-7.5	0.23 ± 0.11	96.2 ± 0.88
F-10	399 ± 1.06	4.81 ± 0.5	5.5-7.5	0.56 ± 0.92	100.1 ± 0.24
F-11	401 ± 0.96	4.82 ± 0.3	5.5-7.5	0.40 ± 0.75	99.6 ± 0.13
F-12	400 ± 0.29	4.84 ± 0.2	5.5-7.5	0.28 ± 0.38	100.6 ± 0.26
F-13	399 ± 1.24	4.83 ± 0.9	5.5-7.5	0.69 ± 0.82	99.8 ± 0.17
F-14	400 ± 0.82	4.84 ± 0.1	5.5-7.5	0.41 ± 0.96	100.1 ± 0.15
F-15	400 ± 1.02	4.88 ± 0.6	5.5-7.5	0.24 ± 0.35	101.2 ± 0.11
F-16	398 ± 1.64	4.82 ± 0.3	5.5-7.5	0.52 ± 0.88	100.3 ± 0.04
F-17	400 ± 0.93	4.85 ± 0.8	5.5-7.5	0.27 ± 0.59	99.9 ± 0.10
F-18	400 ± 1.32	4.89 ± 0.3	5.5-7.5	0.51 ± 0.35	99.6 ± 0.54
F-19	398 ± 1.61	4.86 ± 0.4	5.5-7.5	0.46 ± 0.91	100.5 ± 0.3
F-20	400 ± 1.22	4.88 ± 0.9	5.5-7.5	0.59 ± 0.85	99.8 ± 0.16
F-21	400 ± 0.78	4.89 ± 0.1	5.5-7.5	0.52 ± 0.46	100.2 ± 0.08
F-22	398 ± 1.97	4.89 ± 0.2	5.5-7.5	0.27 ± 0.68	98.5 ± 0.12
F-23	400 ± 0.78	4.89 ± 0.8	5.5-7.5	0.18 ± 0.43	100 ± 0.17
F-24	400 ± 0.36	4.89 ± 0.7	5.5-7.5	0.13 ± 0.29	99.2 ± 0.13

*All values are expressed as mean ± SD, n = 3

Table 4: % Cumulative drug release of formulations F1-F24

F	% Drug release in hours								
	1	2	4	6	8	12	16	20	24
F1	25.98 ± 0.64	32.50 ± 0.42	44.45 ± 0.65	58.87 ± 0.52	69.24 ± 0.85	86.29 ± 0.48	101.58 ± 0.74	-	-
F2	23.06 ± 0.58	30.28 ± 0.23	41.67 ± 0.47	53.16 ± 0.62	58.45 ± 0.39	79.87 ± 0.87	91.56 ± 0.42	100.26 ± 0.64	-
F3	20.09 ± 0.82	28.35 ± 0.58	38.61 ± 0.71	46.82 ± 0.67	52.19 ± 0.36	74.69 ± 0.41	85.16 ± 0.74	93.37 ± 0.32	100.12 ± 0.60
F4	28.68 ± 0.51	35.98 ± 0.43	46.24 ± 0.57	59.64 ± 0.62	70.28 ± 0.45	99.62 ± 0.63	-	-	-
F5	26.47 ± 0.89	33.12 ± 0.65	44.32 ± 0.73	54.48 ± 0.19	63.19 ± 1.28	83.62 ± 0.82	100.12 ± 0.24	-	-
F6	23.21 ± 1.12	30.86 ± 0.69	39.42 ± 0.78	48.62 ± 1.24	59.82 ± 0.46	78.92 ± 1.54	95.98 ± 1.14	-	-
F7	22.28 ± 0.42	29.89 ± 0.65	39.28 ± 1.16	56.74 ± 0.69	69.18 ± 1.32	85.83 ± 0.82	98.54 ± 0.28	-	-
F8	18.56 ± 0.67	25.28 ± 0.52	36.67 ± 0.81	48.54 ± 0.61	56.88 ± 0.26	73.24 ± 0.46	83.81 ± 0.18	91.46 ± 0.26	99.24 ± 0.15
F9	16.12 ± 0.72	22.38 ± 0.45	29.07 ± 0.28	35.29 ± 1.18	42.15 ± 0.35	55.73 ± 1.25	64.95 ± 0.63	72.04 ± 0.92	78.53 ± 0.21
F10	26.46 ± 0.54	32.87 ± 1.45	44.32 ± 0.78	58.84 ± 1.62	69.19 ± 0.41	100.12 ± 0.56	-	-	-
F11	24.21 ± 0.12	29.43 ± 0.35	40.56 ± 0.59	55.17 ± 1.18	64.28 ± 0.92	89.28 ± 0.51	99.06 ± 0.65	-	-
F12	20.09 ± 0.63	25.19 ± 0.156	35.79 ± 0.82	49.12 ± 0.76	58.35 ± 0.89	72.49 ± 0.51	86.48 ± 1.11	99.96 ± 0.42	-
F13	26.43 ± 1.17	34.65 ± 0.82	42.18 ± 0.96	56.29 ± 0.63	70.11 ± 1.43	100.06 ± 0.52	-	-	-
F14	24.02 ± 0.54	30.46 ± 0.92	38.21 ± 1.32	51.85 ± 0.85	64.76 ± 1.28	88.32 ± 0.72	99.32 ± 0.29	-	-
F15	20.18 ± 0.68	27.28 ± 0.154	34.37 ± 0.92	47.54 ± 0.38	59.74 ± 1.12	79.28 ± 0.87	88.10 ± 0.23	99.89 ± 0.85	-
F16	25.98 ± 0.52	30.87 ± 0.69	41.34 ± 0.27	55.36 ± 1.62	69.28 ± 0.95	95.29 ± 0.48	-	-	-
F17	22.65 ± 0.73	27.43 ± 0.97	36.76 ± 1.35	49.71 ± 0.92	58.92 ± 0.69	80.32 ± 0.48	96.21 ± 0.88	-	-
F18	20.12 ± 0.64	25.96 ± 0.87	33.47 ± 0.93	46.28 ± 1.13	55.17 ± 0.59	74.29 ± 0.41	81.97 ± 0.82	98.78 ± 0.29	-
F19	28.68 ± 0.78	37.88 ± 0.52	48.54 ± 0.87	60.24 ± 1.36	70.28 ± 0.94	99.18 ± 0.34	-	-	-
F20	25.37 ± 0.39	31.18 ± 0.61	41.36 ± 0.89	55.26 ± 0.72	64.43 ± 0.98	83.19 ± 0.79	100.05 ± 0.25	-	-
F21	21.02 ± 0.42	27.65 ± 1.52	36.21 ± 0.68	51.31 ± 1.16	59.29 ± 0.52	76.74 ± 1.24	89.52 ± 0.62	99.67 ± 0.39	-
F22	22.28 ± 0.49	29.89 ± 0.73	39.28 ± 0.88	56.74 ± 0.44	69.18 ± 1.18	85.83 ± 0.55	98.54 ± 0.28	-	-
F23	20.18 ± 0.62	26.02 ± 0.89	37.86 ± 1.54	49.29 ± 0.93	57.43 ± 1.08	75.18 ± 0.91	86.27 ± 0.32	99.86 ± 0.17	-
F24	17.56 ± 0.28	23.16 ± 0.51	35.24 ± 0.83	43.65 ± 1.04	52.17 ± 0.72	69.34 ± 0.38	77.82 ± 0.27	85.13 ± 0.43	94.72 ± 0.19
MP	19.30 ± 0.35	25.73 ± 0.58	36.56 ± 0.21	47.63 ± 0.39	55.75 ± 0.72	73.85 ± 0.81	84.42 ± 0.69	92.45 ± 0.25	98.32 ± 0.14

Figure 1: *In-vitro* Dissolution Profile For Batches F1 – F12 Figure 2: *In-vitro* Dissolution Profile For Batches F1 – F24 Figure 3: Comparison of *In-vitro* drug release graph of Reference and optimized formulation (F8)

The % drug content for all the formulations were close to 100 and varied between 96.2 to 101.06% indicating consistency in the manufacturing process. *In-vitro* drug release study of formulation F3 containing combination of Carbopol 971 P and Hpmck4M polymers has sustained up to 24 h. And formulation F24 containing combination of Carbopol 971P and Xanthan gum polymers has sustained up to 24 h and they were formulated with 35 % concentrations. Formulation F8 prepared with Combination of Carbopol 971 P and HPMC K15M polymers has successfully extended the model drug release up to 24 h and they were formulated at 25 % concentration only. All formulations compared with the marketed product for drug release pattern and were matched using similarity factor 86.76 (f_2); which showed that formulation F8 performed similar to the marketed product therapeutically. Based on the evaluation results the formulation F-8 containing Combination of Carbopol 971 P and HPMCK15M polymers were selected as best formulation. Different kinetic models were applied to the optimized formulation and observed that F-8 followed first order kinetic model and it was complied with Reference sample. The best linearity was found in Korsmeyer-peppas model (where $n = 0.542$ is the release exponent); Applicability of data indicating Non Fickian diffusion (or) Anomalous Transport as mechanism of drug release. Non Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. The stability study for the selected formulation of F-8 was performed as per ICH guidelines. Stability study is carried out for 3 months at 40°C; 75 % RH, according to ICH guidelines. The tablets were tested for release during the stability period and confirmed that results were found within the limits.

CONCLUSION

From the results of the present study experiment, it was concluded that the optimized Formulation F-8 formulated with Combination of Carbopol 971 P and HPMCK15M as the polymers has sustained the Itopride Hydrochloride release up

to 24 h at 25 % concentration only. Excipients used in the formulation reduce the cost, which are available at lower price in market. The study includes development of the robust and stable product, which complies with the marketed product.

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