ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of intragastric hydrodynamic balanced system of itopride hydrochloride

Santhosh Kumar M*, Ajaykumar Patil, Ramakrishna R, Dana SB, Vijay kumar N

Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Beside L.M.D Police Station, Karimnagar – 505 481, Andhra Pradesh, India.

ABSTRACT

Itopride hydrochloride, which is better absorbed in stomach and upper small intestine, was formulated as hydrodynamic balanced tablet using gas generating agent (sodium bicarbonate),hydrophilic polymer (different grades of hydroxy propyl methylcellulose) and drug release retarding agent (Eudragit RSPO),with an objective to control the drug release and restrict the region of drug release to stomach. Tablets were prepared by direct compression method and the compression force of the machine was adjusted to obtain the hardness of 4kg/cm^2 and 6kg/cm^{2}for different batches. The stability of the drug in the formulations was confirmed by FTIR studies. Thickness and diameter of all the formulated tablets were in the range of 4.14 to 4.61mm and 12.02 to 12.25mm respectively. All the formulations showed good buoyancy time (8-12h). Swelling study indicates that swelling of the tablet increases with respective to time and directly proportional to the viscosity of the polymer. *In vitro* drug release studies of the tablets indicated controlled release for itopride hydrochloride. The tablet containing Drug: HPMC E15 in 1:2 ratios (F_{12}) showed better controlled release over a period of 12h with the 74.26% drug release. Hence it is evident from this investigation that gas powered hydrodynamic balanced tablet could be promising delivery system for itropride hydrochloride with controlled release action and improved drug bioavailability.

Key words: Itropride hydrochloride, hydrodynamic, swelling study, HPMC, Eudragit RSPO.

*Corresponding author
E-mail: inspiration.santosh@gmail.com
Mobile - + (91)9985931385

ISSN: 0975-8585

INTRODUCTION

The gastric emptying time has been reported to be from 2-6h in humans in the fed state. When a sustained release dosage form is administered orally, sufficient bioavailability could not be obtained, especially for drugs having a limited absorption site in the intestinal tract. Therefore modern oral controlled release dosage forms must be based on gastrointestinal physiology, so that the drug is fully available for absorption [1]. Itopride hydrochloride is a novel gastroprokinetic, widely absorbed from the stomach and upper part of the small intestine and absorption becomes less as the drug passes beyond this. The bioavailability can be improved by making the drug completely absorbed in the stomach and upper part of the small intestine. It has a half life of 6h [2]. The short half life of Itopride hydrochloride necessitates frequent administration. Therefore it is highly desirable to have a controlled release dosage form for Itopride hydrochloride. The objective of this present investigation was to formulate hydrodynamic balanced tablet of itopride hydrochloride using a gas generating agent. We attempted to formulate to retain the matrix tablet in the stomach and subsequently to provide delivery of the drug over the period of time of GRT.

MATERIALS AND METHODS

Itopride hydrochloride, Eudragit RSPO, HPMC E15 and Aerosil were obtained as a gift sample from Hetero Drugs Ltd., Hyderabad. HPMC K4M, HPMC K15M were obtained as a gift sample from Micro Labs., Bangalore. Sodium bicarbonate and dicalcium phosphate were obtained from S.D. Fine Chem. Ltd. Mumbai. All other chemicals and solvents used were of analytical reagent grade.

Formulation of Itopride hydrochloride hydrodynamic balanced tablets

Hydrodynamic balanced tablets of itopride hydrochloride were prepared by direct compression method using sodium bicarbonate as gas generating agent and water soluble polymer (different grades of HPMC) as hydrophilic matrix in each formulation. The composition of formulation is given in the Table 1. Based on the trial bases the compositions of the formulation were made by using different swellable polymers to float more than 5 h. HPMC used as swellable polymer i.e. to float but not to retard the release. All the ingredients except aerosil were blended in glass mortar uniformly. After sufficient mixing of drug as well as other excepients, aerosil was added and further mixed for additional 2-3m. Powder thus obtained was compressed into tablets on a 10 station single punch rotary tablet compression machine (Rimek). A flat-faced punch 12mm in diameter was used for tableting. Compression force of the machine was adjusted to obtain the hardness of 4 kg/cm^2 and 6 kg/cm^2 for different batches.

Evaluation of hydrodynamic balanced tablets

The prepared hydrodynamic balanced tablets were evaluated for weight variation, thickness, buoyancy, and *in vitro* release characteristics. All the formulations were subjected to detailed dissolution study. The hardness of the tablets was measured by Monsanto hardness tester and thickness of the tablets was measured by using Vernier calipers.

Stability studies

The stability of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of the pure and all the formulations were determined using Shimadzu FTIR spectrophotometer by KBr disc method.

Buoyancy determination

Buoyancy time was determined by using USP XXIV paddle dissolution apparatus [3], at 100rpm using 900ml of 0.1N HCl and temperature was maintained at 37±0.5°C throughout the study. The duration of buoyancy (buoyancy time) is the time the tablet floats in the dissolution medium (including buoyancy lag time).

ISSN: 0975-8585

Swelling Study [4]

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of per cent weight gain, as given by the equation.

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} \times 100$$

W_2 = Weight of dosage form at time t.
W_1 = Initial weight of dosage form

In vitro drug release studies

The *in vitro* release studies were carried by using fabricated equipment called Modified Rossett-Rice test [5]. Tablet was placed in the modified beaker containing 100ml of 0.1NHCl at 37±0.5°C and at 75rpm. 5ml of the sample was collected at regular intervals for 12h and the same volume of fresh medium was added. The samples withdrawn were filtered and drug content in each sample was analysed after suitable dilution by Elico UV/Visible spectrophotometer at 249nm.

RESULTS AND DISCUSSION

The physical parameters (thickness and diameter), buoyancy time, drug content and *in vitro* drug release of all the formulation are shown in Table 2. The thickness of the tablets prepared was in the range of 4.14 to 4.61mm and the diameter was in the range of 12.02 to 12.25mm. FTIR spectra analytical reports confirmed that there was no interaction between drug and excipients used.

Carbon dioxide is formed within the tablet containing effervescent agent when the tablet is brought in contact with the acidic dissolution medium. The low density of hydroxypropyl methylcellulose assists in floating the tablet. Moreover, the gelling capacity of HPMC also helps to float the tablet by entrapping carbon dioxide gas in the gel network of HPMC. The gelling capacity of HPMC prevents disintegration of the tablet during the dissolution study. From the results it can be concluded that the tablets compressed at low compression force showed good buoyancy lag time; this may be due to increase in bulk volume and porosity but total buoyancy time is less. The tablets compressed at high compression force showed increased buoyancy lag time; this may be due to reduction in bulk volume and porosity but total buoyancy time is more.

Different grades of HPMC were chosen as swellable polymer because it is widely used as low-density hydrocolloid system, upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH [6]. Eudragit RSPO is used in combination with HPMC to slow the drug release; Eudragit ability to do this may be caused by the low solubility in gastric pH. Sodium bicarbonate is used as gas generating agent which induces floatability of the tablet and it makes tablet remain to float in stomach. Aerosil is used as lubricant and glidant to improve flow property of powder blend. Aerosil also imparts hydrophilic environment and increases wettability of polymers which leads to uniform swelling and uniform drug release.

Swelling index describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups.

From the results it was concluded that swelling increases with respect to time, because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.

ISSN: 0975-8585

Table 1: Formulation of itopride hydrochloride hydrodynamic balanced tablets

Ingredients	Quantity Per Tablet (mg)											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Itopride HCl	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K_4M	150	150	200	200	---	---	---	---	---	---	---	---
HPMC $K_{15}M$	---	---	---	---	150	150	200	200	---	---	---	---
HPMC E_{15}	---	---	---	---	---	---	---	---	150	150	200	200
Eudragit RSPO	30	30	40	40	30	30	40	40	30	30	40	40
Sodium bicarbonate	40	40	40	40	40	40	40	40	40	40	40	40
Di-calcium phosphate	64	64	4	4	64	64	4	4	64	64	4	4
Aerosil	16	16	16	16	16	16	16	16	16	16	16	16
Each tablet weight	400	400	400	400	400	400	400	400	400	400	400	400
Compression force used to get hardness (kg/cm^2)	4	6	4	6	4	6	4	6	4	6	4	6

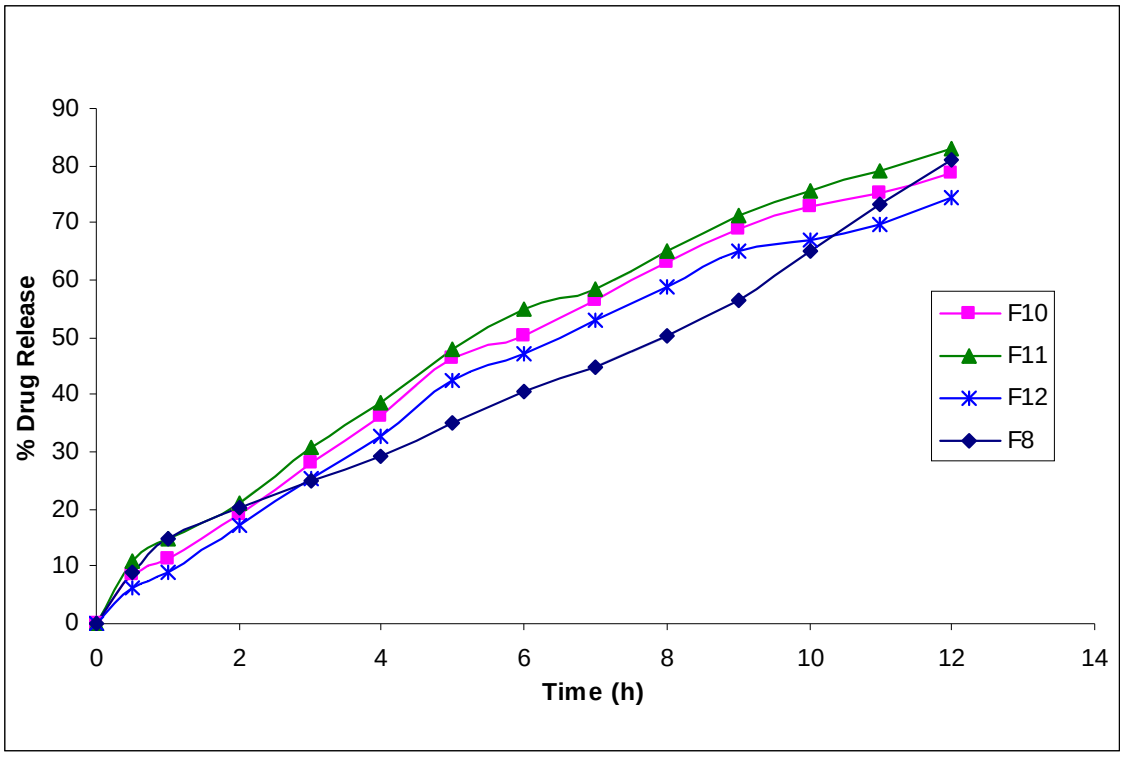

Fig 1: Release Profile of Itopride hydrochloride in 0.1N HCl

ISSN: 0975-8585

Table 2: Evaluation data of hydrodynamic balanced tablet of itopride hydrochloride

Formulation	Buoyancy Lag Time(h) ± SD	Total Buoyancy Time(h) ± SD	Diameter mm ±SD	Thickness mm ±SD	Hardness kg/cm^2 ±SD	Per cent Drug Content ±SD
F_1	0.12 ± 0.04	8.0 ± 0.06	12.12 ± 0.09	4.36 ± 0.12	3.6 ± 0.05	99.78 ± 0.4
F_2	0.14 ± 0.05	9.5 ± 0.03	12.21 ± 0.12	4.14 ± 0.15	5.6 ± 0.07	97.56 ± 0.7
F_3	1.14 ± 0.06	9.0 ± 0.09	12.25 ± 0.11	4.28 ± 0.06	3.6 ± 0.08	99.50 ± 0.5
F_4	0.16 ± 0.03	10.0 ± 0.09	12.02 ± 0.07	4.15 ± 0.13	5.7 ± 0.12	96.85 ± 0.6
F_5	0.09 ± 0.07	9.5 ± 0.08	12.07 ± 0.09	4.61 ± 0.12	3.7 ± 0.11	97.23 ± 0.4
F_6	0.10 ± 0.09	10.5 ± 0.07	12.18 ± 0.11	4.55 ± 0.07	5.8 ± 0.09	98.91 ± 0.8
F_7	0.09 ± 0.06	10.0 ± 0.08	12.15 ± 0.13	4.35 ± 0.09	3.8 ± 0.10	96.98 ± 0.5
F_8	0.10 ± 0.04	11.0 ± 0.06	12.08 ± 0.10	4.18 ± 0.11	5.8 ± 0.07	97.12 ± 0.4
F_9	0.13 ± 0.06	10.0 ± 0.05	12.15 ± 0.09	4.55 ± 0.08	4.0 ± 0.13	98.36 ± 0.7
F_{10}	0.16 ± 0.09	11.5 ± 0.07	12.22 ± 0.06	4.26 ± 0.13	5.9 ± 0.11	98.56 ± 0.5
F_{11}	0.11 ± 0.08	11.0 ± 0.09	12.12 ± 0.10	4.34 ± 0.06	4.1 ± 0.07	99.01 ± 0.6
F_{12}	0.15 ± 0.05	12.0 ± 0.09	12.23 ± 0.11	4.22 ± 0.06	6.1 ± 0.11	98.39 ± 0.4

Table 3*: In vitro* evaluation data of hydrodynamic balanced tablet of itopride hydrochloride

Formulation	Per cent Drug Released			
	3 h	6 h	9 h	12 hrs
F_1	44.06	63.25	78.71	99.190
F_2	30.29	48.59	68.13	88.032
F_3	35.89	53.03	70.27	91.184
F_4	26.92	46.19	65.03	85.723
F_5	38.02	52.14	70.03	88.210
F_6	27.27	42.73	59.61	84.657
F_7	30.11	46.99	63.60	86.078
F_8	25.05	40.60	56.59	81.015
F_9	36.95	56.14	73.38	87.233
F_{10}	27.98	50.19	69.11	78.883
F_{11}	30.74	54.99	71.24	82.969
F_{12}	25.49	47.17	65.03	74.263

In the present study, the higher swelling index was found for tablets containing HPMC $K_{15}M$ having nominal viscosity of 15,000 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

The drug release profile of the tablets having total buoyancy time of 11h or more are shown in Fig 1.

Among all the formulations, formulation F_{12} contains polymer HPMC E_{15} (Drug: Polymer in 1:2 ratio) compressed to get 6 kg/cm^2 hardness showed maximum release retardation with total buoyancy time of 12h Table 3.

In conclusion, controlled release hydrodynamic balanced tablets can be prepared by incorporating sodium bicarbonate as gas generating agent in HPMC E_{15} and Eudragit RSPO.

ACKNOWLEDGEMENTS

The authors are thankful to Prof. R. Ramakrishna, Principal, Vaageswari Institute of Pharmaceutical Sciences, for providing the necessary facility.

REFERENCES

[1] Shyamala B and Harsha. The Eastern Pharmacist 2001; 44: 105.
[2] Seema G Kapoor V and Kapoor B. JK Science 2004; 6: 106.
[3] The United States Pharmacopoeia 24th Edn. Pharmacopoeial Convention, Inc., Rockvillie. MD., USA, 2000, 1942.
[4] Patel VM, Prajapati BG and Patel MM. AAPS Pharm Sci Tech 2007; 8(1): Article 22.
[5] Gohel CM, Mehta RP, Dave KR and Bariya HN. Dissolution technologies 2004; 1: 22.
[6] Narendra C, Srinath MS and Babu G. AAPS Pharm Sci Tech 2006; 7(2): Article 34.