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Formulation and analytical method development for simultaneous estimation of domperidone and itopride from sustained release matrix tablet

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ABSTRACT

Sustained Release matrix tablet containing 20mg domperidone and itopride 50 mg were prepared by wet granulation method. Formulation F5 exhibited best drug release, i.e. about 20% drugs were released in 2 hours to give therapeutic effect and sustained the release up to about 12 hours. No drug polymer interaction was observed from IR studies and stability study data shows that the formulation F5 can be stable up to minimum 2 years. UV spectrophotometric scan had been carried out for the determination of maximum wavelength (λ_{max}) of domperidone and itopride. It is revealed that the λ_{max} of itopride and domperidone was at 259 nm and 285 nm respectively and the HPLC parameters for the simultaneous determination of domperidone and itopride was as follows: 10 m.mol Potassium dihydrogen phosphate buffer of pH 6.0: acetonitrile = 60: 40 (v/v) Column: C 18, 250 X 4.6 mm, 5 µm particle size, λ_{max} : 270nm, Flow rate: 1ml/min. where the retention time of itopride and domperidone was found to be 2.077 and 4.167 min, respectively.

Keywords: Domperidone, itopride, sustained release tablet.

INTRODUCTION

Gastro esophageal reflux disease (GERD), or acid reflux disease, is a common health problem that causes heartburn and acid regurgitation from the stomach. GERD has been regarded as chronic-relapsing disease like hypertension and diabetes mellitus. Among several therapeutic drugs, a prokinetic agent has been used for the treatment and improvement of pathogenic mechanism of GERD such as gastrointestinal motility disorder, incompetent LES relaxation, impaired esophageal acid clearance, and prolonged gastric emptying. Among the kinds of prokinetic drugs, many studies have focused on the effect of drugs on GERD (Agid Y, Pollak P, Bonnet AM.**1979** Lancet 1(8116): 570-572). In one of them, itopride increases tones of esophageal peristalsis and LES dose-dependency in healthy subjects. Dual mechanism of itopride, acetylcholine esterase inhibitory action and week antagonistic activity on dopamine D receptor, which is known to inhibit seems to make this drug effective on promoting the esophageal and gastrointestinal movement and on improving acid clearance. Prokinetic drugs that inhibit dopamine D receptor may elicit some adverse events such as fatigue, confusion, extra pyramidal symptom, and hyperprolactinemia that cause lacteal secretion or breast enlargement (Banka NH.**2003**. Rol of pro in dys GasTod 7:1-4). Although there was no extensive study concerned about safety of itopride, the development of extra pyramidal symptom or hyperprolactinemia was uncommon with the administration. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. The antiemetic properties of domperidone are related to its strong dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level (Barone JA.**1998** Hosp Pharm 33(2): 191 -197).

Therefore, the combination of itopride and domperidone can be useful for treatment of the patients with GERD. As the half life of both the drugs are relatively low (4-6 hours).The combination of sustained released drug is effective for better management of GERD and gatromotility symptoms. In the present study, two different drugs domperidone and itopride with different mode of action were selected to prepare a bi-layer matrix tablet as sustained release (SR) dose of both drugs (Bose A, Bhaumik U, et al.**2009**, Chromatographia 69:1233-1241).

MATERIALS AND METHODS

Instrument

The HPLC system used was Jassco liquid chromatography equipped with 2075 PLUS, UV/Visible detector & PU-2080 PLUS pump. Auto-sampler: Smartline 3800 Software: Eurochrom 2000

Reagents and Chemicals

Itopride Hcl was purchase from Theon Pharmaceuticals Pvt. Ltd., HP Domperidone Provided by Emcee Pharmaceuticals Pvt. Ltd., Kolkata. HPMC K100 M, PVPK 30, Aerosil, Magnesium stearate Di basic calcium phosphate was Provided by Stadmed Pvt. Ltd., Kolkata. Were as HPLC grade water Obtained from in-house Milli-Q system of Millipore (Elix 3, Milli-Q A10 Academic).And Acetonitrile, Methanol were Procured from Spectrochem Pvt. Ltd., Mumbai. KH_2PO_4, Ethyl acetate, Hcl, Formic acid, Borax were provided by Merck India Ltd., Mumbai.

Preparation of Solutions

Preparation of Domperidone and Itopride hydrochloride Standard Stock Solutions

Accurately weighed quantity of 10 mg each of Domperidone and itopride was transferred to a 100mL volumetric flask, These stock solutions were further diluted with mobile phase to produce standard solution of 1, 2, 4, 6, 8 and 10 µg/ml for each of domperidone and itopride HCl and these solutions were analyzed by HPLC (A.H.Beckett, J.B.Stenlake ,Pract Pharma Chem, Par II,4th edn, CBS Publications,**1997**,Page No. 275 & Tasnuva H, Singh S et al, j pharm biomedanal **2007**; 41:1037-40).

Development of sustained release matrix tablet containing 20 mg domperidone and 50 mg itopride HCl In the present work, an attempt has been made to formulate the extended release matrix tablets of domperidone and itopride using different ratio of HPMC polymer and PVP K30 formulations containing 20 mg domperidone and 50 mg itopride were developed as shown in Table1. HPMC E5 5% was used as binder. The granules were formulated according to wet granulation method. All the raw drugs and excipients were passed through 40 mesh size sieve separately. Active drugs, the polymers and dibasic calcium phosphate were mixed thoroughly. The mixing product was passed through the 20 mesh size sieve. The granules were dried at 40^0 C in oven dryer for 30 minutes. The granules thus formed were also passed through 18 mesh size sieve. The granules were then mixed with lubricating agent Aerosil and magnesium state before compression (Nagaraju R,Kaza R, Int jou of phar sci & nano**2009**;vol.2 & Kartheikeyini CS, Int.J.ChemTech.Res.**2009**; 1(4):1381-1385).

Table 1: Composition of formulations with different ratios of polymer

Formulation Code / Composition	F1	F2	F3	F4	F5	F6
Domperidone	20	20	20	20	20	20
Itopride hydrochloride	50	50	50	50	50	50
HPMC K100 M	0	10	20	30	40	50
PVP K30	50	40	30	20	10	0
Dibasic calcium phosphate	25	25	25	25	25	25
HPMC E5	5	5	5	5	5	5
Aerosil	2.0	2.0	2.0	2.0	2.0	2.0
Erythrosine yellow	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of pre-compression parameters

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is determined by the funnel method. Angle of repose less than 300 shows the free flowing of the material. Angle of repose was determined by the following formula: Angle of repose = tan Φ × 2h/D where d is the diameter of pile and h is the height of pile

(Martin, A, 2001. Physical Pharmacy, Lippincott Williams & Wilkins, P 423-454) (Kartheikeyini CS, Int.J.ChemTech.Res.2009;1(4):1381-1385).

Bulk density

Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as g/cm3: Bulk density = mass of powder /bulk volume of powder (Prasanthi NL, Asian J.Pharma.Clin.Res.2010;3(2):104-105.23).

Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow. It is given by % compressibility and calculated as C= (tnb)/ t × 100

Where t is the tapped density and b is the untapped bulk density (N.G.Raghav rao, A. yadav, Int jou of cur phar res 2010;2(1):pp 34-42).

Total porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V) (Martin, 2001) (Mandal U, Pal TK, Drug Dev Ind Pharm. 2008 Mar; 34(3):305-13).

Porosity (%) = $V_{bulk} - V/V_{bulk}$ X 100

Evaluation of Tablets

The tablets were characterized immediately after the formulation. The weight variation was carried out taking 20 tablets according to guideline mentioned in I.P 1996 using electronic balance. Friability was evaluated using 10 tablets by Roche type friabilator for 4 min at the rate of 25 rpm. For each formulation the hardness of 10 tablets was evaluated using Monsanto handness tester (chambell electronics, India). The thickness of the 10 tablets was measured by electronic Varner caliper (mitutoyo, Japan). The formulations being sustained release matrix tablet, there was no scope for disintegration test (The British Pharmacopoeia crown copy right, 2005; 5thEd. 1303-1304, 2588-2589, A133) (The United State of Pharmacopoeia 24/ Nf19 Asian Edition) (Indian Pharmacopeia 1996).

Assay of SR matrix tablet containing itopride HCl and domperidone

20 tablets of the sustained formulation were crushed into fine powder by mortar and pastle. 100mg of the crushed powder was weighed in 100ml volumetric flask and diluted upto the mark with methanol. After sonication for 15 minutes, the diluted solution was filtered. Again after the proper dilution of test solution, the total amount for drug for each tablet was analyzed. by using the HPLC method as described in the section 4.3 against the calibration curve prepared from reference solution. As we have chosen the HPLC method for sample analysis, there is no chance of detection of any degradation products (Trinath M, Seshachalam U, J liq chromatogratech 2010;31(5):714–21).

Dissolution study of matrix tablet

Drug releases of individually 6 tablets were measured using USP 1 (basket type) apparatus (Electrolab, TDPOGP, USPxxiii) using 900ml 0.1 (N) HCl as dissolution media at a rotation speed 100 rpm. The dissolution medium was maintained at 37 ±0.5°Cthroughout the study. The sample was withdrawn at the interval of 0.5, 1, 1.5, 2, 4, 6, 8, 10 & 12 hr according to preprogrammed manner. At every withdrawn the sample was replaced with 5ml of fresh media. The release rate of tablets were evaluated in a dissolution medium 0.1 (N) HCl for 12 hr. all the solution of samples were analyzed by using high performance liquid chromatography (HPLC) method as described in section Instrument (Nagaraju R, Kaza R, Int jou of pharm sci and nano 2009;vol.2).

RESULTS AND DISCUSSION

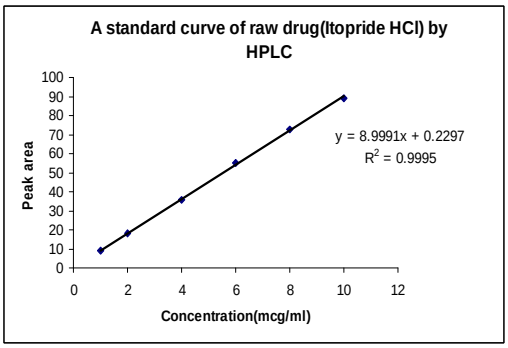
Chromatographic analysis of SR matrix tablet

Maximum UV absorption of domperidone and itopride were found at 285 nm and 259 nm respectively.

Selection of wavelength for simultaneous analysis of domperidone and itopride HCl by HPLC

Itopride and domperidone have maximum UV absorption at different wavelengths. But, a single wave length was needed for the simultaneous analysis of itopride and domperidone by HPLC. As both the drugs have got enough absorption at 270 nm this was selected for determination of both the drugs.

Preparation of standard calibration curves for raw drugs of domperidone and itopride



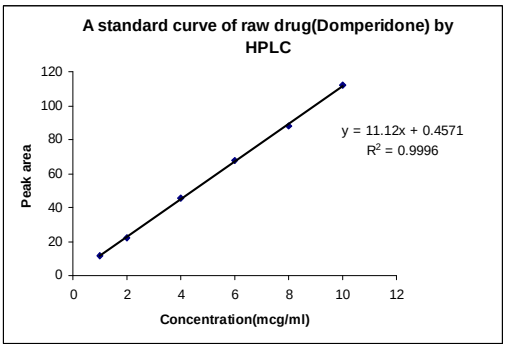


Figure: 1 A Standard Curve of Row drug(Itopride HCl) by HPLC **Figure: 2 A Standard Curve of Row drug(Domperidone) by HPLC**

Table 2: Evaluation of pre-compression parameter

Pre-compression parameters

Formulation No.	Angle of repose	Loose bulk density (gm/ml)	Tapped bulk density (gm/ml)	Compressibility index (%)	Total porosity (%)
F1	24.12±0.23	0.545±0.03	0.651±0.19	15.38±0.09	24.05±0.23
F2	26.58±0.43	0.535±0.15	0.642±0.34	13.11±0.11	22.29±0.21
F3	26.70±0.08	0.532±0.05	0.654±0.22	15.34±0.06	23.13±0.21
F4	24.44±0.11	0.534±0.09	0.696±0.12	14.41±0.11	24.12±0.12
F5	25.45±0.36	0.516±0.05	0.612±0.12	13.23±0.61	20.54±0.25
F6	27.35±0.62	0.521±0.04	0.652±0.23	15.49±0.09	26.09±0.32

Micromeritic properties of domperidone and itopride granules which are illustrated in Table 2 Were found to be within normal limit.

Evaluation of Tablets

All the formulated tablets containing the active drugs were evaluated to find the physical properties like hardness, thickness, friability and drug contents. All the formulation should uniform thickness. The property of thickness is important for packaging purpose. In a weight variation test, the Pharmacopeial limit of percentage deviation for tablets whose weight is more than 250 mg is ±5%. The average percentage deviation of all the tablets were found within the limit which was less than1%.Hardness of the tablets were found acceptable and uniform from batch to batch variation. The drug content was also found uniform and within the prescribed limit.

Table 3: Evaluation of Tablet

Formulation No.	Friability (%)	Hardness(kg/ cm^2)	Thickness(mm)	Drug Content (%)
F1	0.31±0.13	4.3±0.06	4.5±0.07	97.09±0.12
F2	0.55±0.04	4.3±0.12	4.6±0.18	94.03±0.12
F3	0.41±0.08	5.2±0.03	4.6±0.07	97.07±0.03
F4	0.26±.02	5.1±0.07	4.6±0.13	99.12±0.12
F5	0.38±0.10	5.4±0.09	4.4±0.09	98.04±0.10
F6	0.41±0.12	5.3±0.11	4.7±0.13	95.09±0.12

Chromatographic analysis

Dissolution samples were analyzed by **HPLC-UV method** Figure 3 shows the representative chromatogram of a dissolution sample showing separation of domperidone and itopride HCl at retention time 2.077 and 4.167 min respectively.

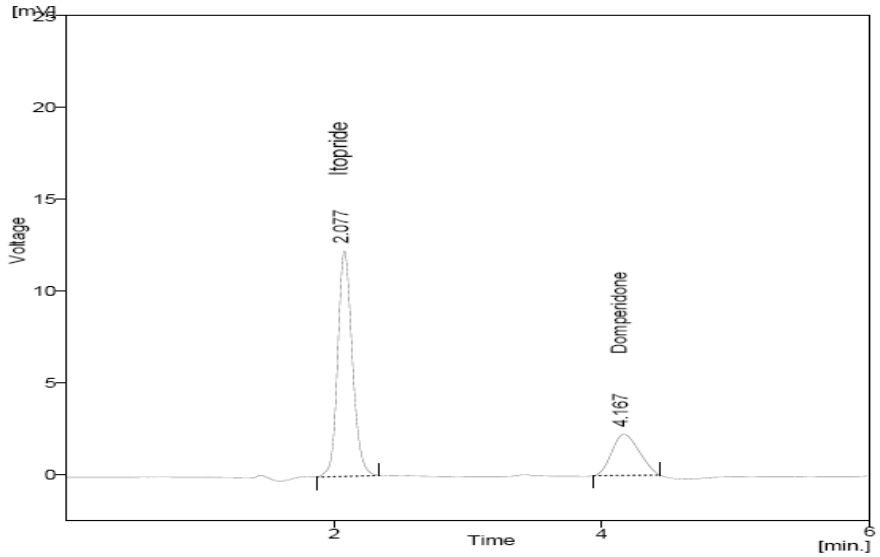


Figure: 3 chromatogram showing separation of itopride & domperidone

Figure: 3 Representative chromatogram showing separation of itopride at 2.077 and domperidone at 4.167 min.

In vitro release of domperidone and itopride from SR matrix tablet

Dissolution study was carried out to determine the release of domperidone and itopride HCl from SR matrix tablet. The dissolution profile for both drugs was found to be different from batch to batch. But the formulation of F5 was found to be most desired release profile for both the drugs having most consistent, accurate and complete for domperidone, itopride.

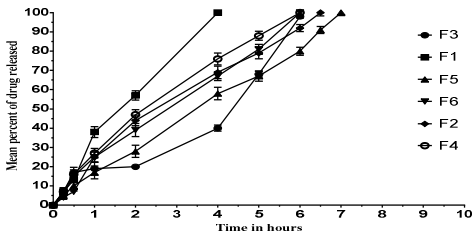


Figure: 4 Mean cumulative % drug release (domperidone) profile of matrix formulations

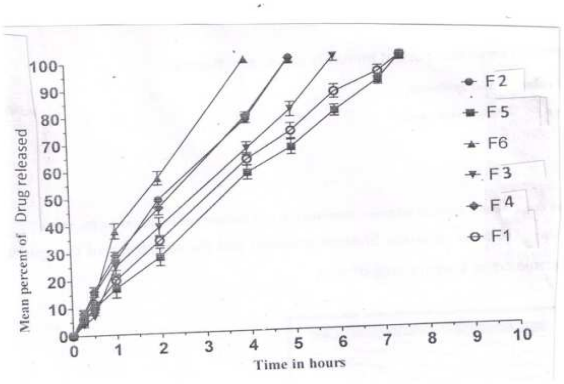


Figure: 5 Mean cumulative % drug release (itopride)
Profile of matrix formulations

CONCLUSION

Sustained release tablet was formulated using wet granulation, and Formulation F5 exhibited best drug release, i.e. about 20% drugs were released in 2 hours to give therapeutic effect and sustained the release up to about 12 hours. An efficient high performance liquid chromatographic method was developed for Domperidone and Itopride. The retention time of itopride and domperidone was found to be 2.077 and 4.167 min, respectively. This work can be further extended to study the applicability of this method to determine Domperidone and Itopride in bulk drugs.

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