ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 8, Issue 6, 2015

ISSN - 0974-2441

Research Article

CONTROLLED RELEASE LAYERED MATRIX TABLETS OF ITOPRIDE HYDROCHLORIDE: *IN VITRO* AND *IN VIVO* EVALUATION

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Received: 12 July 2015, Revised and Accepted: 09 September 2015

ABSTRACT

Objectives: The tablets were prepared by wet granulation method using polyethylene oxide, which was used to prepare both the matrix core and barrier layers. *In vitro* dissolution studies were carried out on the developed formulations. Based on the dissolution data, the best formulation was chosen, and evaluated for its controlled release in healthy human volunteers.

Results: When the dissolution data was analyzed, IMP3L2 has shown the highest R^2 value (0.9866) with at least 80% of the drug released in 12 hrs among all the formulations. Hence, the formulation IMP3L2 was chosen as an ideal formulation and selected for *in vivo* studies in human volunteers. Eight healthy volunteers participated in the study, and a two-way crossover design was followed. The serum concentration of itopride hydrochloride was estimated by reverse-phase high-performance liquid chromatography. The pharmacokinetic parameters were calculated from the serum concentration of itopride hydrochloride versus time data. The delayed T_{max}, decreased K_a, unaltered bioavailability, and prolonged $t_{½}$, indicated a slow and prolonged release of itopride hydrochloride from polyethylene oxide layered matrix tablets in comparison with the plain matrix tablet.

Conclusion: Based on the results of *in vitro* and *in vivo* studies, it was concluded that polyethylene oxide based layered matrix tablets provided oral controlled release of itopride hydrochloride.

Objective: In this study, layered matrix tablets of itopride hydrochloride were formulated using polyethylene oxide as release retardant to achieve a zero order drug release. The objective of the study was to develop a formulation which will release at least 80% of the drug in 12 hrs and show a correlation coefficient (R^2) value of at least 0.95.

Keywords: Layered matrix tablets, Itopride hydrochloride, Polyethylene oxide, High-performance liquid chromatography, Serum.

INTRODUCTION

Controlled release drug delivery is one of the frontier areas of formulation development, which provides continuous therapeutic efficacy. These dosage forms require once or twice a day administration instead of frequent dosing intervals for a particular drug. This greatly improves patient compliance and adherence to drug therapy.

Hydrophilic polymers are more popular in formulating oral controlled release dosage forms currently available [1-3]. As the dissolution medium or biological fluid penetrates, the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer, as well as formulation technology.

It is well-documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time-dependent profile [4-6]. This is because before the polymer(s) begin to swell and control the release rate of drug, a significant portion of drug, located close to the surface, can dissolve leading to high release rate. The release of a dissolved drug inherently follows near first-order diffusion with an initially high release rate, due to the dissolution of the drug present at the surface of the matrix, followed by a rapidly declining drug release rate [7].

To overcome this undesirable behavior, many authors [8,9] evaluated a number of variables able to affect the release patterns in polymeric matrix devices such as physicochemical properties (solubility, viscosity, etc.); content of drugs and polymers; drug/polymer weight ratio; administration form; and dosage and manufacturing process to achieve a constant rate release. Over the years, considerable efforts have been expended in the development of new drug delivery concepts to achieve zero-order or near zero-order release since constant rate delivery is the primary goal of controlled release systems. Various matrix geometries have been recommended over the last two decades to achieve an almost constant release rate of the drug with time. One of these techniques relies on the use of multi-layered matrix tablets as drug delivery devices.

Multi-layered matrix tablet is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during the tableting process. The modulating layers delay the interaction of an active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate [10].

In this device, the coat layers prevent the water penetration, through the protected core for some duration. This results in reduced hydration rate and controlled area for solute release at the core. Thus, burst effect can be smoothened, and the release can be maintained at a relatively constant level during the barrier layers' swelling and erosion process. After this phase, during the subsequent portion of the dissolution process, these swollen barriers are erosion dominated, and the surface available for drug release slowly increases. In this way, the decrease of delivery rate due to the increase of diffusion path-length (saturation effect) is counterbalanced by the simultaneous increase of the area available for drug release [11]. By this way, combining a time-dependent control of the hydration rate of the device with the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear release profile.

Itopride HCl, a gastric prokinetc agent [12], is a water-soluble drug and having short biological half-life (3.66 hrs) hence considered as

a suitable candidate for CR drug delivery systems. It is used in the treatment of chronic gastritis, gastrointestinal reflux disease, and diabetic gastroparesis where long-term therapy is required. Because of the high solubility, short half-life and therapeutic use in chronic diseases, the above drug is considered as ideal drug candidates for the design of oral controlled release dosage forms and is used in this study. In the present study Polyethylene oxide, WSR 303 (Polyox) was used as a hydrophilic polymer.

METHODS

Materials

Itopride hydrochloride and nimesulide were gift samples from Sun Pharmaceuticals and Alembic limited, Vadodara India. Polyethylene oxide WSR 303 (Polyox) was purchased from HiMedia, Mumbai. Polyvinyl pyrrolidone (PVP) and isopropyl alcohol (IPA) were obtained from Loba Chemie, Mumbai and Nice Chemicals, Cochin. Microcrystalline cellulose, (AvicelPH-101), starch, magnesium stearate, and talc used were of USP/NF quality. Acetonitrile (high-performance liquid chromatography [HPLC] grade) and diethyl ether (chromatography grade) were purchased from Merck, Mumbai whereas potassium dihydrogen orthophosphate (HPLC grade) and sodium bircarbonate (AR grade) were purchased from HiMedia, Mumbai.

Preparation of itopride hydrochloride plain matrix tablets

Plain matrix tablets were prepared by wet granulation method. A mixture of talc and magnesium stearate (2:1 ratio) was used as lubricant, and microcrystalline cellulose was used as a diluent. Polyox were used in the formulations in various proportions (20-40%) as polymer excipient. The drug substance, diluent, and the polymers were passed through the sieve ≠ 60 separately. Required quantities of drug, polymers and diluent were mixed in various ratios as shown in Table 1 to get a homogenous powder mixture. The powder mix was granulated with 4% PVP dispersion in IPA based on the total weight of the tablet. The wet mass was passed through sieve ≠ 12 to get the wet granules which were then air dried to obtain dried granules. The dried granules were screened through sieve ≠ 14 to get uniform size dried granules, and these granules were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed into tablets on a Cadmach single punch machine using 10 mm round and flat punches. The three formulations were coded as IMP1, IMP2, and IMP3.

Preparation of itopride hydrochloride layered matrix tablets

The preparation of the layered matrix tablets involved the following steps:

1. Preparation of granules for active matrix core
2. Preparation of layer forming polymer granules
3. Compression of layers (50 mg) of polymer granules on one or both sides of the granules active matrix core.

The granules for the active matrix core were prepared in a similar fashion as described for the plain matrix tablets. Polymer granules were prepared by blending the polymer and the diluent with 4% dispersion PVP in IPA to obtain a wet mass. The resulting wet mass was passed through sieve No. 12, and the granules were then air dried. The dried granules were screened through sieve 14 to get uniform granules. These granules were lubricated with a mixture of talc and magnesium stearate (2:1 ratio).

Table 1: Formulation of itopride hydrochloride plain matrix tablets with Polyox

Ingredients (mg)	Formulations		
	IMP1	IMP2	IMP3
Itopride HCl	75	75	75
Polyox	50	75	100
Avicel PH 101	107.5	82.5	57.5
PVP	10	10	10
Talc	5	5	5
Magnesium stearate	2.5	2.5	2.5

Weight of each tablet 250 mg. PVP: Polyvinyl pyrrolidone

The two- or three-layer tablets were prepared by progressive hand filling of the die with weighed amounts of the different granulates. Layered tablets were prepared by following method: the ingredients for the barrier layer were placed in the die and compressed slightly. The ingredients for the active core layer were then added and compressed into the tablet in case of two-layer tablets. In case of three-layered tablets the middle layer was also compressed slightly and finally, the ingredients for the top layer were added, and the whole assemblage was compressed. The compression force was set to obtain a hardness of about 6-8 kg. The layered formulations were coded as IMP1L1, IMP2L1, and IMP3L1 for two-layered tablets whereas IMP1L2, IMP2L2, and IMP3L2 for three-layered tablets.

In vitro drug release studies

The plain and layered matrix tablets were subjected to *in vitro* drug release studies for 12 hrs to assess their ability in providing the desired controlled drug delivery. Drug release studies were performed on a USP 26 dissolution rate test apparatus I (basket). The dissolution medium was 900 ml of double distilled water, maintained at 37°C±0.5°C. The basket rotation speed was set at 100 rpm. An aliquot of 5 ml sample was withdrawn at predetermined time intervals and replaced with an equal volume of the fresh dissolution medium to maintain the total volume constant. The samples were filtered and suitably diluted, and the amount of drug released was determined spectrophotometrically at 258 nm.

Kinetic analysis

The cumulative amount of drug released from the plain matrix tablets and layered matrix tablets at different time intervals was fitted to zero order kinetics using the least square method. It is a method of analysis to find out whether the drug release from the formulations is providing a constant drug release. The correlation coefficient between the time and cumulative amount of drug released were also calculated to find the fitness of the data to zero order kinetics. The zero order kinetics [13] is described as:

$$Q_t = Q_0 + K_0.t$$

Where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times $Q_0=0$) and K_0 is the zero order release constant.

The dissolution profile was considered as:

- Zero-order if $R^2 \geq 0.975$
- Near zero-order if $0.950 < R^2 < 0.975$
- No zero-order if $R^2 \leq 0.950$.

Only those formulations having both a sustained (>80% drug release after 12 hrs) and zero-order ($R^2 \geq 0.975$) drug release profile were considered as good formulations.

The data were also subjected to following models [14-16]:
First order kinetics: $\ln Q_t = \ln Q_0 + K_1.t$
Higuchi model: $Q = K.t^{½}$
Korsmeyer and Peppas: $M_t/M\alpha = kt^n$

Where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution, K_1 is the first order release constant, Q is cumulative drug release from matrix tablets, K is the dissolution rate constant, t is time, $M_t/M\alpha$ = The fraction drug release, t = Release time, k = A constant depending on the structural and geometric characteristics of the release device, n = The time exponent indicative of the release mechanism (if n=0.5: Fickian diffusion, 0.5<n<1: Non-Fickian diffusion, n=1: Case II transport and in n>1: Super Case II transport).

Stability studies

The selected formulations were subjected to the accelerated stability studies as per ICH guidelines (40°C±2°C and 75%±5% RH) for a period of 6 months in humidity chamber (Thermolab, Mumbai, India). The samples (n=3) were taken out at 30, 60, 90, and 180 days and evaluated for physical appearance, drug content and release characteristics. The protocol of the stability studies was in accordance with the recommendation in WHO document for stability testing of products intended for global market [17].

***In vivo* pharmacokinetic evaluation in human volunteers**

A total of eight healthy human male volunteers aged between 22 and 35 years, gave written informed consent to participate in the study, the protocol of which was approved by the Institutional Ethics Committee of Roland Institute of Pharmaceutical Sciences, Berhampur, India (Approval number: IEC/01). All the volunteers participated in the study were non-smokers and did not drink alcohol. The nature and purpose of the study, and its possible consequences were fully explained to them. An informed written consent was obtained from every volunteer. None of the volunteers were on drug treatment 1 week prior to participation in the study. The volunteers were free to withdraw from the study at their discretion. This study was a cross-over single-dose two-period study which compares the absorption pattern of itopride hydrochloride from two dosage forms: IMP3 and IMP3L2 tablets, administrated orally, under fasting conditions. The volunteers were divided into two equal groups (Group I and Group II), and a crossover study was followed. Group I was administered with IMP3 tablets whereas Group II was administered with IMP3L2 tablets. After a washout period of 1 week, Group I volunteers received IMP3L2 tablets and Group II volunteers received the IMP3 tablets. Both tablet formulations were administered with 240 ml of water after a 12 hrs overnight fast. Food and drinks were withheld for at least 2 hrs after dosing. Blood samples were collected by direct venipuncture using a catheter hep lock over a period of 30 hrs (0, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 30 hrs). The serum was separated, transferred to the labeled tubes and were stored at −20°C, until analyzed.

HPLC analysis of itopride hydrochloride in human serum

Collection of serum [18]

Freshly, drawn blood was allowed to stand for 1-2 hrs at room temperature for clot formation. The clot was carefully separated from the wall of the tube with an applicator stick and then the tube was stored in a refrigerator for 12-24 hrs to permit clot contraction. The supernatant was decanted into a clean tube and was centrifuged at 2500 rpm at about 4°C for 30 minutes, and the serum was carefully removed from the tube using a micropipette. Since it is always desirable to have very clear serum, and often the serum from the first centrifugation contains a few erythrocytes or white cells, these cells were removed by repeated centrifugation as described above, to collect a clear serum free from cells.

Determination of itopride in serum samples

The quantitative determination of itopride hydrochloride was performed on an HPLC system consisting of LC-10AT and LC-10AT VP series pumps with SPD-10A ultraviolet-visible Spectrophotometric detector. The output signal was monitored and integrated using CLASS-VP Version 6.12 SPI software from Shimadzu Corporation, Japan. Liquid-liquid extraction was performed by adding 50 µl of internal standard (10 µg/ml) and 50 µl of 0.1 M sodium bicarbonate to 500 µl of human serum samples followed by addition of 2.0 ml of diethyl ether. The sample was vortexed for 3.0 minutes and allowed to settle for 10.0 minutes. About 1.0 ml of the supernatant was transferred to another test tube and was evaporated to dryness in a thermostatically controlled water bath maintained at 40°C for 20 minutes. After drying, the residue was reconstituted with 200 µl of the mobile phase. 20 µl of reconstituted sample was injected into an ODS–C_{18} column (25 cm × 4.6 mm) with 5 µ particle size with a mobile phase (acetonitrile: 0.05 M KH_2PO_4, 50:50 v/v) flowing through it at a flow rate of 1.0 ml/minutes. Itopride and nimesulide (internal standard) were detected at a wavelength of 258 nm.

Pharmacokinetic calculations

The maximum plasma concentration (C_{max}) and the time required to reach C_{max} (T_{max}) were directly read from the arithmetic plot of time versus serum concentration of itopride hydrochloride. The overall elimination rate constant (k_e) was calculated from the slope of the terminal elimination phase of a semilogarithmic plot of concentration versus time after subjecting it to linear regression analysis. The elimination half-life ($t_{½}$) was obtained by dividing 0.693 with k_e. The absorption rate constant (k_a) was calculated using the method of residuals [19]. The mean residence time (MRT) was calculated as described below.

Determination of MRT

The tendency of the drugs to remain in the body can be assessed by measuring the MRT. Assuming that the drug in the organs of elimination is always in equilibrium with the drug in plasma, the MRT can be defined as the average amount of time spent by drug molecules in the body before being eliminated. If one considers time course of drug concentration in plasma as statistical distribution curve, Yamoka *et al*. [20] showed that:

$$MRT = AUMC/AUC$$

Where, AUMC is the area under the "first-moment curve" and is obtained from the plot of the product of drug concentration in plasma and time versus time from zero to infinity as described by Chung [21].

$$AUMC = \int_0^\infty C.t.dt$$

AUC is the area under the "zero-moment curve" and is obtained by plotting the drug concentration in plasma versus time from zero to infinity.

$$AUC = \int_0^\infty C.dt$$

The MRT is considered as the statistical moment analogy to half-life. It represents the time for 63.2% of the administered dose to be eliminated.

Determination of dosage form index

The goodness of controlled release formulation can be evaluated by dosage form index (DI).

$$DI = C_{max}/C_{24} \text{ or } C_{max}/C_{30}$$

The parameter DI was determined to compare the degree of fluctuation [22,23] as far as the release profile is considered. The closer the ratio to unity, the less the serum drug concentration fluctuations and higher the therapeutic efficacy of dosage form. The higher the value, the release is non-linear. Always lower degree of fluctuation is desired.

Statistical analysis

The observed variation in the pharmacokinetic parameters such as $t_{½}$, K_a and MRT was tested using analysis of variance with the help of Graph Pad Prism Software 4.00 version, 2003. The observed difference between mean pharmacokinetic parameters of itopride hydrochloride from layered and plain matrix tablets was subjected to paired t-test to find the statistical significance. In all the cases, a value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

***In vitro* study**

The itopride hydrochloride plain and layered matrix tablets were prepared using wet granulation method and subjected to *in vitro* drug release studies in distilled water for 12 hrs on an eight-stage dissolution

test apparatus (DISSO 2000, Lab India) using 900 ml of dissolution medium, maintained at 37°C±0.5°C. The tablets were placed in the cylindrical basket and set to rotate at 100 rpm. The obtained data has been treated to assess the drug release kinetics. From the dissolution data; it was observed that as the polymer concentration increases, rate of drug release decreases in all the formulations. However, all of them showed an initial high release (around 50-64%) within 2 hrs (Fig. 1). This high release could be due to the exposure of the entire tablet surface to the dissolution medium.

The correlation coefficient (R^2) was determined from the plot "percentage drug release versus time." The R^2 value for zero order ranged from 0.7032 to 0.8075 indicating that the drug release from the plain matrix tablets does not follow zero first order kinetics (Table 2).

In case of Polyox tablets, the R^2 values for two-layered tablets were found to be <0.95 indicating that, they could not provide linear release. But in case of three-layered formulations the R^2 values of the release data were ranging from 0.9636 to 0.9866, suggesting that the formulations IMP1L2, IMP2L2, and IMP3L2 could control the release of the drug, which following near zero order in case of IMP1L2 and zero order in case of IMP2L2 and IMP3L2**.**

The dissolution data were further characterized by fitting them in the Higuchi's square root time model. The correlation coefficient values of Higuchi plot ranges from 0.95 to 0.99 for Polyox plain and layered matrix tablets. As the correlation coefficient values are close to one, it can be said that the drug release was by diffusion mechanism.

When the percent of itopride hydrochloride released was plotted against time on log-log scale, the diffusional exponents' values (n) ranged from 0.34 to 0.36 for plain matrix tablet indicating that itopride hydrochloride release from Polyox matrices followed Fickian diffusion. Even the value of "n" for two-layer tablets was <0.5 (0.33-0.45) indicating Fickian diffusion. But the "n" values for three-layered tablets were found to be more than 0.5 (0.73-0.79) indicating that these tablets followed non-Fickian diffusion.

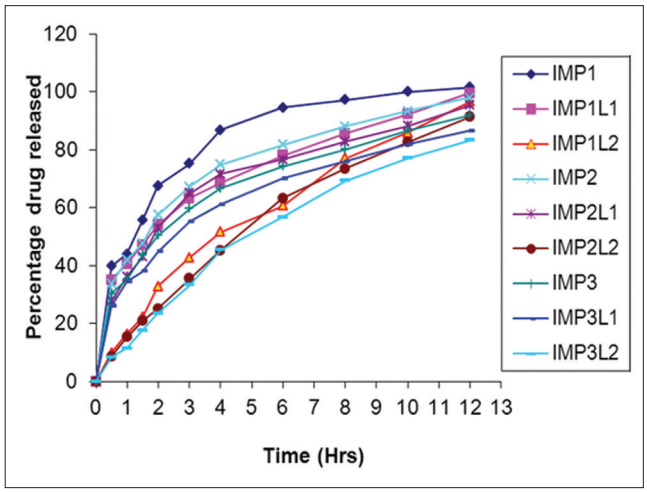

Fig. 1: *In vitro* dissolution profiles of plain and layered matrix tablets

Table 2: *In vitro* dissolution kinetics of itopride hydrochloride plain and three-layer matrix tablets with Polyox

Formulation	Zero order correlation coefficient (R^2)	Higuchi's coefficient	Diffusional exponent
IMP1	0.7032	0.9533	0.34
IMP1L1	0.8052	0.9822	0.34
IMP1L2	0.9636	0.9916	0.73
IMP2	0.7715	0.9746	0.34
IMP2L1	0.8425	0.9897	0.39
IMP2L2	0.9776	0.9883	0.76
IMP3	0.8075	0.9832	0.36
IMP3L1	0.9127	0.9984	0.45
IMP3L2	0.9866	0.9836	0.79

Selection of the best formulation

The objective of the study was to develop a formulation which will release at least 80% of the drug in 12 hrs and show an R^2 value of at least 0.95. In case of Polyox layered tablets, all the formulations released more than 80% of the drug in 12 hrs. The R^2 values of two-layered tablets were found to be <0.95; hence these formulations failed to meet the selection criteria (Table 3). Out of all the three-layered formulations, IMP3L2 released more than 80% of the drug at the end of 12 hrs with maximum R^2 value, i.e. 0.9866 compared to other two- three-layered formulations, therefore IMP3L2 was considered to be the best formulation when compared to all other formulations and is said to follow zero order kinetics. Hence, this formulation (IMP3L2) is selected for further studies (stability and bioavailability studies).

Stability studies

The stability studies of the optimized three-layer matrix tablet IMP3L2 was conducted to assess its stability with respect to their physical appearance, drug content, and drug release characteristics. The results of the accelerated stability studies indicated that the tablets showed no change in physical appearance during the study period. The drug content was found to be above 95% in case of IMP3L2 at the end of 180 days (Table 4). There was no observed difference in the dissolution pattern of the formulation IMP3L2 before and after a storage period. This indicates that the optimized formulation is fairly stable.

In vivo pharmacokinetic evaluation

Serum itopride hydrochloride concentrations at different time intervals were determined and the mean serum concentration time profile of itopride hydrochloride is shown in Fig. 2 following a single oral dose of the plain matrix tablet (IMP3) and layered matrix tablet (IMP3L2) to eight volunteers in two Groups A and B, each composed of four volunteers. Bioavailability parameter estimates of the study are given in Table 5.

Table 3: Comparison of R^2 values and percentage drug released in 12 hrs of itopride hydrochloride plain and three-layer matrix tablets with Polyox

Formulation	R^2	Percentage drug released in 12 hrs
IMP1	0.7032	99.86
IMP1L1	0.8052	97.55
IMP1L2	0.9636	97.2
IMP2	0.7715	97.99
IMP2L1	0.8425	95.38
IMP2L2	0.9776	96.36
IMP3	0.8075	91.96
IMP3L1	0.9127	93.23
IMP3L2	0.9866	92.06

Table 4: Stability studies of the optimized itopride hydrochloride formulations with Polyox

Time period	Percentage drug content of IMP3L2	
	Mean (n=3)	SD
0 days	97.37	0.86
30 days	96.83	1.01
60 days	96.47	0.85
90 days	96.4	2.79
180 days	95.93	0.76

SD: Standard deviation

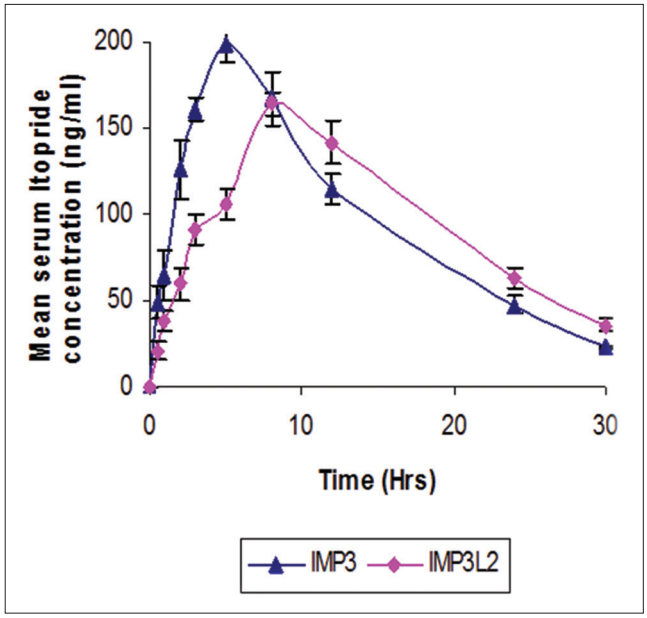

Fig. 2: Mean serum levels of itopride hydrochloride following administration (mean±standard deviation) from plain (IMP3) and layered (IMP3L2) matrix tablets

Table 5: Mean (±SD) pharmacokinetic parameters of the itopride hydrochloride plain (IMP3) and layered matrix tablets (IMP3L2) from different volunteers (n=8)

Pharmacokinetic parameter	Formulation	
	IMP3	IMP3L2
C_{max} (ng/ml)	197.9±8.48	164.5±6.09
k_e (1/hrs)	0.08±0.008	0.067±0.005
$t_{½}$ (hrs)	8.19±0.861	10.47±0.873
$AUC_{0-\infty}$ (ng/ml/hrs)	3647.42±157.73	3521.89±112.601
MRT	11.91±0.513	14.19±0.669
k_a (1/hrs)	0.078±0.007	0.049±0.005

MRT: Mean residence time

The mean C_{max} values were found to be 197.9±8.48 ng/ml and 164.5±6.09 ng/ml and T_{max} values were about 5 hrs and 8 hrs for IMP3 and IMP3L2, respectively. It was apparent that prolonged absorption was achieved with both the matrices. More rapid early absorption observed for the single layer matrix tablet can be attributed to higher initial release due to non-linear release, as well as overall higher release rate when compared to the layered matrix tablet. The absorption rate constant (K_a) of the drug from plain matrix tablet is 0.078±0.007/hrs and that obtained from layered matrix tablet is 0.049±0.005/hrs, and the difference in the value of absorption rate constant is statistically significant. Thus, the prolonged T_{max} and decreased K_a of itopride hydrochloride in case of layered tablets indicated that the drug release is retarded, providing a prolonged and controlled *in vivo* delivery.

The $AUC_{0-\infty}$ was found to be 3647.42±157.73 and 3521.89±112.6 for IMP3 and IMP3L2 respectively. As there is no significant difference between the $AUC_{0-\infty}$ of plain and layered matrix tablets, it can be said that the bioavailability of itopride hydrochloride from both the matrices is almost similar. The elimination half-lives ($t_{½}$) of itopride hydrochloride following oral ingestion of the plain and layered matrix tablet were 8.19±0.86 and 10.47±0.87 hrs respectively, which are statistically significant. Thus, the prolonged $t_{½}$ indicates that the release from the layered tablet is slow compared to that of the plain matrix tablet.

The MRT of itopride hydrochloride of the plain and layered matrix tablet was 11.91±0.512 and 14.19±0.67 hrs respectively, which are statistically significant. These results indicate that in case of layered tablet the drug stays for more time in the body when compared to plain matrix tablet as the drug is slowly released from the layered tablet compared to that of the plain matrix tablet. There is no significant difference in the pharmacokinetic parameters when the plain matrix tablet was administered to both the groups. Similar is the case found with layered tablets also except $t_{½}$ which shown a significant difference. But the error is very marginal (p=0.0481). The relatively higher degree of fluctuation resulting from non-linear release was indirectly indicated by the fact that the C_{max}/C_{24} ratio of plain matrix tablet was significantly higher than those of layered matrix tablets (p=0.0014 for Group A and 0.0075 for Group B). The present study demonstrated the successful preparation of a "twice daily" controlled release tablet of itopride hydrochloride.

CONCLUSIONS

The present study was carried out to develop oral controlled delivery systems for itopride hydrochloride using Polyox as a carrier. Polyox matrix tablets containing various proportions of polymers were prepared and subjected to *in vitro* drug release studies. Plain matrix formulations could not provide the linear release of itopride hydrochloride and also unable to control initial high drug release. Hence, layered matrix tablets with either one or two-layers of respective polymers were subjected to *in vitro* drug release studies. Formulations containing 40% of Polyox and two-layers (IMP3 L2) were found to provide the best linear release profile as compared to other formulations. These optimized three-layer matrix tablets after storing at 40°C/75% RH for 6 months showed no change either in physical appearance or drug content. The *in vivo* evaluation of Polyox three-layer matrix tablets of itopride hydrochloride in human volunteers showed delayed T_{max}, decreased K_a, unaltered bioavailability, and prolonged $t_{½}$, indicating a slow and prolonged release of the drug from Polyox three-layer matrix tablets compared to that of plain matrix tablet. Based on the results of *in vitro* and *in vivo* studies it was concluded that that polyethylene oxide based layered matrix tablets provided oral controlled release of itopride hydrochloride.

ACKNOWLEDGMENTS

The authors greatly acknowledge M/s Sun Pharmaceuticals, India, and M/s Alembic Ltd., India, for the gift samples of itorpide hydrochloride and nimesulide, respectively. The authors also wish to thank M/s. Roland Institute of Pharmaceutical Sciences for providing necessary research facilities.

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