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Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology

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Abstract

Extended release formulations of isosorbide mononitrate (IMN), based on osmotic technology, were developed. Target release profile was selected and different variables were optimized to achieve the same. Formulation variables like type (PVP, PEG-4000, and HPMC) and level of pore former (0–55%, w/w of polymer), percent weight gain were found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the initial level of pore former in the membrane. Burst strength of the exhausted shells was inversely proportional to the level of pore former, but directly affected by the membrane weight. Satisfactory burst strength (more than 320 g) was obtained when PVP was used as pore former (up to 55%, w/w of polymer) at the membrane weight of 7.5% and more. The release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The formulations were found to be stable after 3 months of accelerated stability studies. Prediction of steady-state levels showed the plasma concentrations of IMN to be within the desired range.

Keywords: Coating; Extended release; Isosorbide mononitrate; Osmotic pressure; Osmotic pump; Stability

1. Introduction

Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance, and convenience. In immediate-release (IR) dosage forms, there is little or no control over release of drug from the dosage form, which most often results in constantly changing, unpredictable, and often sub- or supra-therapeutic plasma concentration. Recently, there has been considerable interest in the development of novel drug delivery systems (NDDS) and number of products based on newer drug delivery technologies has increased significantly (Verma and Garg, 2001). Among the various NDDS available, *per oral* controlled release (CR) systems hold the major market share because of their advantages of ease of administration and better patient compliance (Speers and Bonnano, 1999).

A number of design options are available to control or modulate the drug release from a dosage form. Majority of the oral dosage forms fall in the category

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of matrix, reservoir, or osmotic systems. Osmotic systems utilize the principles of osmotic pressure for controlled delivery of drugs (Verma et al., 2000). Drug release from these systems is independent of pH and other physiological parameters to a large extent (Theeuwes, 1975; Theeuwes et al., 1985; Verma et al., 2002). The development of oral osmotic systems has a strong market potential, as evident from the marketed products (Verma and Garg, 2001) and number of patents granted in the last few years (Santus and Baker, 1995).

Isosorbide mononitrate (IMN), an organic nitrate, is mainly indicated for the treatment of stable and unstable angina pectoris, acute myocardial infarction, and heart failure (Parker and Parker, 1998). It offers several therapeutic advantages over other organic nitrates, such as good oral absorption, long elimination half-life (4–5 h) in comparison to ISDN (Abshagen et al., 1981), and absence of first pass metabolism (Jonsson, 1987). Despite longer elimination half-life, IMN is prescribed 2–3 times per day for the prophylactic treatment of angina pectoris (Bonn, 1988). A frequent dosage schedule for patients on long-term medication often leads to poor patient compliance. Moreover, tolerance develops if it is taken in a regular fashion (Parker and Parker, 1998). Tolerance can be avoided by giving IMN in an eccentric fashion (Amsterdam, 1992; Thadani and Bittar, 1992; Parker, 1993) but it may further cause patient inconvenience. Thus, there is a therapeutic need to develop a delivery system that will release IMN in a controlled manner for a definite period of time and thus, produce a dependable plasma concentration–time profile so as to avoid development of tolerance (Kendall, 1990; Gunasekara and Noble, 1999).

The present study was aimed towards the development of extended release formulations of IMN based on osmotic technology. A theoretically designed zero-order delivery pattern was designed to produce plasma levels within the desired range. Different formulation variables were studied and optimized to achieve the desired release profile. The manufacturing procedure was standardized and the stability of the formulations evaluated after 3 months of storage at accelerated stability conditions. Finally, the in vivo performance of the optimized formulation was predicted.

2. Materials and methods

2.1. Materials

IMN (99.9% purity), a gift sample from JP Fine Chemicals, India, was characterized against the working standard of IMN (IMN WS; 99.8% pure), which was obtained as gift sample from Sifa Chemicals, Switzerland. Following chemicals and excipients were purchased from commercial sources and used as such: cellulose acetate (Fluka, Switzerland), ethyl cellulose (Ethocel 10cps, Dow, USA), colloidal silicon dioxide (Aerosil SD-200, Panacea Biotec, India), lactose (Flowlac-100, Meggle, Germany), sodium chloride AR (Loba Chemie, India), polyvinyl pyrrolidone (Plasdone K-29/32, ISP, USA), HPMC (Pharmacoat 606, Shin-Etsu, Japan), PEG-4000 (SD Fine Chemicals, India), propylene glycol (SD Fine Chemicals, India), and magnesium stearate (Mallinckrodt, USA). Dichloromethane-GR (Merck, India) and ethanol (Merck) were used for the preparation of coating solutions. Methanol used for the preparation of mobile phase was of HPLC grade (Ranbaxy, India) and water used throughout the HPLC analysis was prepared by reverse-osmosis (Ultra Pure water system, ELGA, UK).

2.2. Formulation development

Core tablets of IMN were prepared by direct compression and the composition is given in Table 1. The compatibility of IMN with the excipients used for formulation development was tested using the techniques of DSC and isothermal stress testing (Verma, 2002; Verma and Garg, 2002) and all the excipients used were found to be compatible with IMN.

For preparation of core tablets of IMN, the batch size was kept at 150 g. IMN and lactose were mixed

Table 1
Composition of core tablets of IMN

Ingredients	Percent (w/w)
Isosorbide mononitrate	20.00
Lactose	34.18
Sodium chloride	33.32
PVP	10.00
Magnesium stearate	2.00
Colloidal silicon dioxide	0.50

Table 2
Compositions for core tablets of IMN[a]

Code ingredients	IMNOP-4/4	IMNOP-4/5	IMNOP-4/6	IMNOP-4/7	IMNOP-4/8	IMNOP-4/9	IMNOP-4/10
Ethyl cellulose	3.95	3.66	3.30	3.00	2.74	2.74	2.74
HPMC	–	–	–	–	–	1.52	–
PEG-4000	–	–	–	–	–	–	1.52
PVP	–	0.37	0.82	1.20	1.52	–	–
Propylene glycol	1.05	0.98	0.88	0.80	0.73	0.73	0.73
Ethanol	38.00	38.00	38.00	38.00	38.00	38.00	38.00
Dichloromethane	57.00	57.00	57.00	57.00	57.00	57.00	57.00

[a] Compositions given in terms of % (w/w), total solids: 5% (w/w).

for 10 min. After passing this mixture through a 30-mesh sieve, PVP and sodium chloride (30-mesh passed) were added and the mixing continued for additional 10 min. To the mix, 60-mesh passed magnesium stearate and colloidal silicon dioxide (CSD) were added and mixing continued for 10 more minutes. The blend was compressed in the form of biconvex tablets having an average weight of 300 mg using a single stroke tablet-punching machine (CMS-15, Cadmach, India) fitted with 9 mm round standard concave punches. The core tablets of IMN were coated in an automated perforated pan (GAC-250, Ganscoater, India). The composition of coating solution used for coating of IMN tablets is given in Table 2. Various components of the coating solution were added to the solvent mixture in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of IMN were placed in the coating pan. Initially, pan was rotated at low speed (2–5 rpm) and heated air was passed through the tablet bed. Coating process was started once the outlet air temperature reached 28 °C. The rpm of the pan was kept in the range of 15–20 and coating solution was sprayed at the rate of 7–9 ml/min. Atomization pressure was kept at 1 kg/cm^2 and the outlet temperature was maintained above 28 °C by keeping the inlet air temperature in the range of 45–50 °C. Coating was continued until desired weight gain was obtained on the active tablets. In all the cases, active tablets were dried at 50 °C for 16 h before further evaluation.

2.3. Evaluation of the developed formulations

Loss on drying (LOD) of the powder blend was recorded on an IR moisture balance (PM 480, Mettler Toledo, Switzerland). Bulk and tapped density of the powder blend was evaluated using USP method II on a tap density tester (ETD-1020, Electrolab, India) and Compressibility Index and Hausner Ratio were calculated.

The core and coated tablets were evaluated for weight variation. Thickness and diameter of the core and coated tablets was measured using a thickness gauge (Digimatic, Mitutoyo, Japan). Hardness of the randomly selected tablets was tested using hardness tester (TBH-20, Erweka, Germany). Friability of the core tablets was carried out on a friabilator (EF-2, Electrolab, India) for which 20 accurately weighed tablets were used.

The developed formulations ($n = 6$) were subjected to release studies using USP-I dissolution apparatus (Electrolab, India) at 100 rpm. Dissolution medium used was simulated intestinal fluid (SIF, pH 6.8, 900 ml) maintained at 37 ± 0.5 °C. The samples were withdrawn (10 ml) at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples, after filtration through 0.45-μm nylon membrane filters, were analyzed using a validated HPLC method at 220 nm (Verma and Garg, 2002). After analyzing the drug content in the dissolution samples, corrections were made for the volume replacement and the graph of cumulative percentage of drug release versus time was plotted. Release profiles of various formulations were compared using model independent pair-wise approach, which included the calculation of "difference factor" f_1 and "similarity factor" f_2. The two release profiles were considered to be similar; if f_1 value was lower than 15 (between 0 and 15) and f_2 value was more than 50 (between 50 and 100). For the calculation of f_1 and f_2 values, only one data point was taken into consideration after 85% of the drug was released.

Release profiles were also compared using mean dissolution time or MDT, which was calculated using following equation:

$$\mathrm{MDT} = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (1)$$

where j is the sample number, n is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1}, and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1}. One-way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations.

For content uniformity testing, one accurately weighed tablet ($n = 5$) was added in 250 ml of water (Verma and Garg, 2002). The samples were sonicated for 30 min and filtered through 0.45-μm nylon membrane filter. The filtered solutions, after appropriate dilution with the mobile phase, were analyzed at 220 nm using HPLC.

In addition, the developed formulations were subjected to various tests as follows.

2.3.1. Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted in media of different pH (SGF, pH 1.2; acetate buffer, pH 4.5; and SIF, pH 6.8). Dissolution apparatus used was rotating basket type (USP-I) at 100 rpm. The samples (10 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45-μm nylon membrane filters.

2.3.2. Effect of agitational intensity

To study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-I (rotating basket) at 50, 100, and 150 rpm. In another experiment, stirred and stagnant conditions were induced in a single run using USP-I apparatus. The rotational speed was kept at 100 rpm (stirred conditions), which, however, was stopped intermittently to induce the stagnant conditions. The protocol used was stirred conditions for first 3 h (0–3 h), stagnant conditions for next 2 h (3–5 h), stirred condition for next 3 h (5–8 h), and stagnant condition for next 2 h (8–10 h). Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45-μm nylon membrane filters.

2.3.3. Effect of osmotic pressure

To confirm the mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF (Liu et al., 1984; Schultz and Kleinebudde, 1997) and the pH was adjusted to 6.8 ± 0.05. Release studies were carried out in 1000 ml of media using USP-I dissolution apparatus (100 rpm). To avoid any interference in the analysis by sodium chloride, residual drug analysis methodology was utilized for construction of release profile (Appel and Zentner, 1991; Jensen et al., 1995). At predetermined time points, specified numbers of tablets (one or two) were withdrawn from each vessel, cut open, and the contents dissolved in 250–500 ml of SIF. The samples were analyzed to determine the residual amount remaining in each tablet. Accuracy of this method was checked in SIF, where results after direct measurement of IMN into the release media were similar to the results of residual drug analysis method.

2.4. HPLC analysis

For HPLC analysis, Shimadzu HPLC system equipped with LC-10 AT VP pump, DGU-14 AM on-line degasser, SIL-10 AD VP autoinjector, CTO-10 AS VP column oven, and SPD-10 AVP UV-Vis detector was utilized. For peak purity testing, SPD-M 10 A VP PDA detector was used. Shimadzu CLASS-VP software (Version 5.03) was used for data acquisition and mathematical calculations. Chromatographic separation was performed on a C_{18} Spherisorb column (4.6 mm × 250 mm, 5 μm particle size) at 25 °C. The optimized mobile phase composition was water–methanol (80:20, v/v) at a flow rate of 1 ml/min (Verma and Garg, 2002). Detection was performed at 220 nm using a UV detector.

2.5. Osmotic pressure measurement

For the measurement of osmotic pressure of the core formulation, saturated solution was prepared. Excess of drug and the components of the core formulation (in

the weight ratio that was present in the formulation) were added in 5 ml of water (in 30 ml of glass vials). The vials were screw capped tightly and kept for shaking (at 200 rpm) on a shaking water bath at 37 °C for 24 h (Theeuwes et al., 1983, 1985). The samples were filtered through 0.45-μm nylon membrane filter and osmolality measured ($n = 3$) after suitable dilutions, if required, using a vapor pressure osmometer (Vapro, 5520 XR, Vapor pressure osmometer, Wescor, USA). Before measurement, osmometer was calibrated using calibration standards of 100, 290, and 1000 mmol/kg. The osmotic pressure of the dissolution media was also measured in a similar manner.

2.6. Burst strength

Burst strength of the exhausted shells ($n = 6$), after 24 h of dissolution, was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength was determined, as the force required to break/rupture the shells after dissolution studies. The texture analyzer (TAX T2i, Stable Micro systems, England) with a 5 kg load cell and 25 mm aluminum cylindrical probe was utilized for this purpose. Test speed of 0.8 mm/s was selected and the distance moved was set at 2 mm.

2.7. Scanning electron microscopy studies

In order to elucidate the mechanism of drug release from *in house* formulations, surface of coated tablets, both before and after dissolution studies, was studied using scanning electron microscope (SEM). The samples were placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape. The tablets (coated tablets before dissolution studies) were mounted as such on the specimen stub. On the other hand, small sample of the coating membrane was carefully cut from the exhausted shells (after 24 h of dissolution studies) and dried at 50 °C for 12 h. The mounted samples were sputter coated for 5–10 min with gold using fine coat ion sputter (JFC-1100, Jeol, Japan) and examined under SEM (JSM-6100, Jeol, Japan).

2.8. Accelerated stability studies

Optimized formulations of IMN were packed in strips of 0.04 mm thick aluminum foil laminated with PVC. The packed formulations were stored in ICH certified stability chambers (KBF 720, Binder, Germany) maintained at 40 °C and 75% RH for 3 months. The samples were withdrawn periodically and evaluated for drug content, hardness, and release studies.

2.9. Prediction of in vivo performance

Using the known pharmacokinetic properties of drugs (Table 3) and various drug release parameters (R^0 and t_{Del}), which were calculated from in vitro release data, steady-state blood levels of drugs were predicted by the method of superposition (Ritschel, 1989). It was assumed that after the administration of a test dose of formulation, the drug would be released at a release rate (R^0) for a period of time (t_{Del}) shorter than the selected dosing interval (τ). Time of delivery, t_{Del}, is the time taken to deliver 90% of the total drug within a selected dosing interval ($\tau = 24$ h).

The predicted steady-state plasma levels of *in house* formulations were compared with the desired levels by calculating the percent-predicted error (% PD) in $C_{ss\,max}$ and $AUC_{0-\tau}$. Bioequivalence was anticipated

Table 3
Important pharmacokinetic parameters of IMN

Pharmacokinetic parameter	Value	Reference
Fraction of drug absorbed (f)	0.93–1	Benet et al. (1996)
Elimination half-life ($t_{1/2}$) (h)	4.4 ± 0.5	Chasseaud (1987)
Terminal disposition rate constant (k_{el} or β) (h^{-1})	0.16 ± 0.015	Chasseaud (1987)
Apparent volume of distribution (V_d) (l/kg)	48.5 ± 6.1	Chasseaud (1987)
Fraction of unchanged drug excreted in urine (f_{el}) (%)	<5	Benet et al. (1996)
Extent of protein binding in plasma (%)	3.5	Ritschel (1992)
Clearance (CL) (ml/min)	127 ± 21	Chasseaud (1987)

(Sheskey et al., 1999, 2000), if the average % PD was less than 15% for $C_{ss\,max}$ and $AUC_{0-\tau}$. The % PD was calculated using following equation:

$$\%\,PD = \frac{\text{predicted value} - \text{reference value}}{\text{reference value}} \times 100 \quad (2)$$

3. Results and discussion

3.1. Desired drug release profile

The purpose of this study was to select a release profile that could be used as a target for *in house* formulations of IMN. In US market, Imdur (Schering/Key Pharmaceuticals, USA) is recognized as a Reference Listed Drug (Electronic Orange Book, 2002). The maximum steady-state plasma concentration ($C_{ss\,max}$) for Imdur has been reported to be in the range of 557–572 ng/ml (Gunasekara and Noble, 1999). Therefore, the desired maximum steady-state concentration, $C_{ss\,max\,des}$, was selected as 565 ng/ml. During the course of nitrate therapy, plasma concentration should fall to a certain level before a next dose is given (Bonn, 1988; Neugebauer et al., 1989; Nyberg, 1990; Jahnchen, 1992; Stockis et al., 2002). This "intentional fluctuation" is required to avoid the development of tolerance. It is desirable that the plasma levels of IMN should fall to less than 100 ng/ml before the next dose is given (Neugebauer et al., 1989; Kendall, 1990; Wagner et al., 1990; Thadani and Bittar, 1992; Stockis et al., 2002). Keeping this point into consideration, desired minimum steady-state concentration, $C_{ss\,min\,des}$, was kept as 65 ng/ml. Taking different pharmacokinetic parameters of IMN into consideration (Table 3), a zero-order based delivery strategy was designed to produce the desired plasma levels (Ritschel, 1989). Series of simulations (using Microsoft Excel 2000) were performed and it was found that a delivery rate of 5.278 mg/h for a period of 10.48 h was found to meet the above requirements. The simulated plasma concentration–time profile using this approach and the corresponding in vitro drug release profile is shown in Fig. 1. Since, this delivery pattern was expected to maintain plasma levels of IMN within desired range and also close to those produced by Imdur (Schering/Key Pharmaceuticals), it was selected as target release profile.

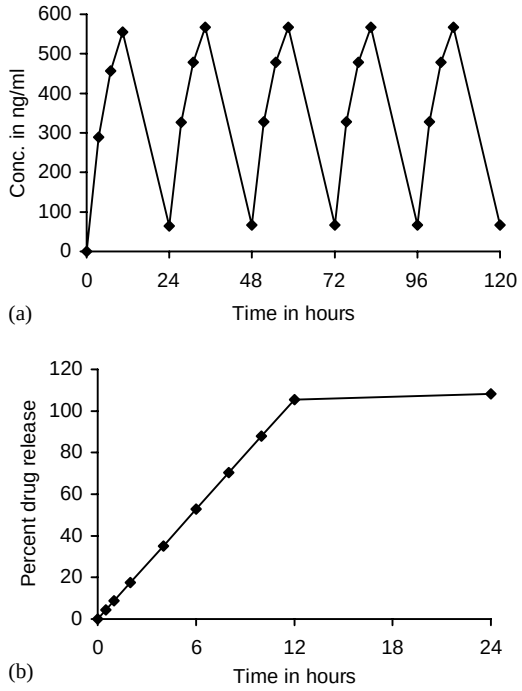


Fig. 1. Predicted steady-state plasma levels of IMN using a theoretically designed zero-order delivery approach (a) and the corresponding drug release profile (b).

3.2. Formulation development

The dosage form developed consists of a tablet core of IMN along with other excipients. IMN has a propensity to generate static electricity and it may also exhibit a sublimation phenomenon during processing (Rossi and Calanchi, 1989; Bougaret and Sournac, 1994; Sanghvi et al., 1998). These special handling considerations require premixing of the drug with an inert carrier, which is generally dry blended with IMN. For this purpose, lactose was used as a diluent. In addition, dosage form consists of osmagents and other conventional excipients so as to form the core compartment. Sodium chloride was used as an osmagent. The tablet core is surrounded by a rate controlling membrane that consists of semipermeable membrane forming polymer, water-soluble additive(s), and plasticizer(s) capable of improving film formation properties of the polymers. Cellulose acetate and ethyl cellulose were tried as water-insoluble polymers. Results of DSC and IST studies showed IMN and

cellulose acetate to be incompatible. Therefore, ethyl cellulose was used in the development of extended release formulations of IMN. PVP, HPMC, and PEG-4000 were tried as water-soluble additives. Propylene glycol was used as a plasticizer. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and the dissolved drug is released from the pores formed in the membrane after leaching of water-soluble additive.

Formulation development involved trials with different types of polymers, water-soluble additives, etc. Following parameters were studied.

3.2.1. Effect of level of pore former

To study the effect of level of pore former (PVP), core tablets of IMN were coated with coating composition containing 0–55% (w/w) of PVP (formulations: IMNOP-4/4 to IMNOP-4/8, Table 2). It was found that the drug release increases with the level of PVP (Fig. 2). As the level of pore former increases, the membrane becomes more porous after coming in contact with the aqueous environment, resulting in faster drug release. Other workers have also obtained similar results (Zentner et al., 1985; Appel and Zentner, 1991; Okimoto et al., 1999). The level of pore former also affected the extent of drug release. Maximum drug release after 24 h was less than 6% in formulations containing up to 25% (w/w) of PVP and around 20% from formulations with 40% (w/w) of PVP. In case of formulations with 55% of PVP, more than 90% of the drug release took place in 12 h. As the pore former level increases, the membrane becomes porous after coming in contact with the water (when the pore former leaches out of the membrane). At levels up to 40% (w/w) of pore former, numbers of pores are not sufficient to contribute to significant drug release. On the other hand, membranes that initially contained 55% (w/w) of pore former; the membrane becomes more porous after coming in contact with water (see SEM in Fig. 17). The explainable reason for the sudden change in the release profile may be that the threshold might not have reached in formulations containing 40% and less of pore former. Therefore, it can be concluded that drug release is directly proportional to the level of pore former in the membrane and this parameter can be varied to control the drug release.

Another parameter affected by the level of pore former was burst strength of the exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in level of PVP, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports (Appel and Zentner, 1991; Appel et al., 1992; Jensen et al., 1995). The effect of level of PVP on burst strength and extent of drug release is shown in Fig. 3. Since, satisfactory drug release and adequate burst strength were obtained in case of formulations with 55% pore former level (IMNOP-4/8), this concentration was selected for further studies.

3.2.2. Effect of weight gain

To study the effect of weight gain of the membrane, coating on the core tablets of IMN was continued for sufficient duration so as to get tablets with different

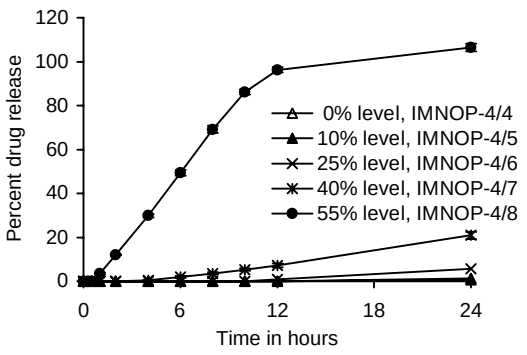


Fig. 2. Effect of level of PVP on IMN release from the developed formulations.

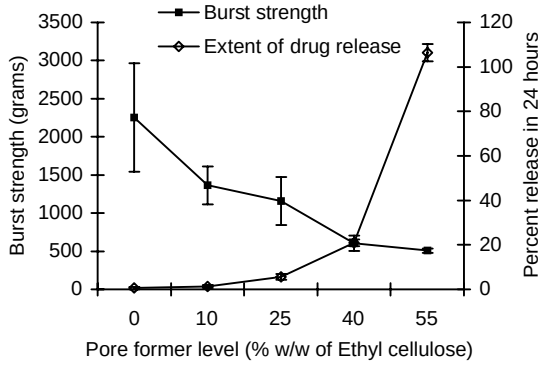


Fig. 3. Effect of level of PVP on burst strength and extent of drug release ($n = 6$).

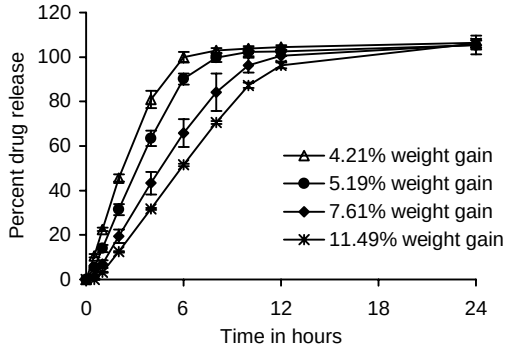


Fig. 4. Effect of weight gain on IMN release from the developed formulations.

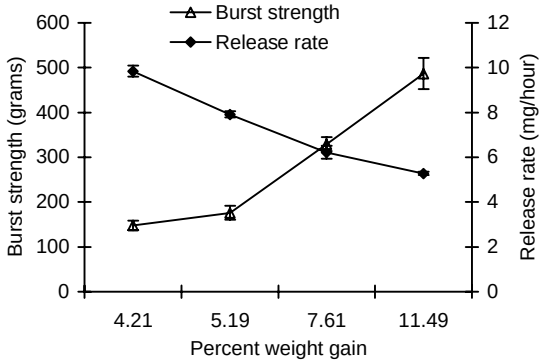


Fig. 6. Effect of weight gain on burst strength and release rate ($n = 6$).

weight gains (4.21, 5.19, 7.61, and 11.49%). Release profile of IMN as a function of weight gain of the membrane is shown in Fig. 4. $MDT_{90\%}$ between the different formulations (2.47, 3.32, 4.63, and 5.77 h for formulations with weight gain of 4.21, 5.19, 7.61, and 11.49%, respectively) was found to be statistically significant ($P \leq 0.001$). Drug release was found to decrease with an increase in the weight gain of the membrane. Fig. 5 shows the release rate as a function of reciprocal of membrane weight. The relationship was found to be linear and is consistent with the results obtained by other workers (Swanson et al., 1987; Ramakrishna and Mishra, 2002). Fig. 6 shows the dependence of burst strength of the exhausted shells and release rate as a function of weight gain. Burst strength was found to be directly proportional to the weight gain of the membrane. No bursting of the systems was observed during the dissolution run in any of the formulations. However, satisfactory burst strength (more than 320 g) was obtained in the membranes with weight gain of more than 7.5%.

3.2.3. *Effect of type of pore former*

To study the effect of type of pore former, formulations IMNOP-4/8, IMNOP-4/9, and IMNOP-4/10 were prepared by coating core tablets of IMN with coating compositions containing different pore formers (PVP, HPMC, and PEG-4000, respectively). As evident from Fig. 7, the type of pore former affected drug release and it is possible to achieve the desired release by using different types and/or combination of pore formers. $MDT_{50\%}$ was found to be 9.31, 5.38, and 3.36 h for formulations containing HPMC, PEG-4000, and PVP, respectively. There was statistically significant difference ($P \leq 0.05$) between the different formulations. In addition to release, type of pore former also affected the burst strength of the exhausted

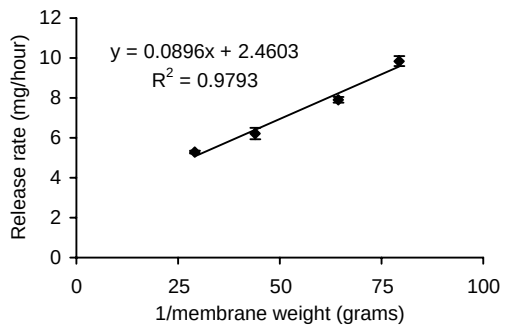


Fig. 5. Effect of weight gain on IMN release rate as a function of membrane weight.

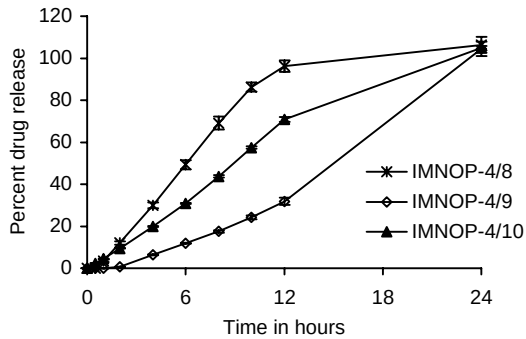


Fig. 7. Effect of type of pore former on IMN release from the developed formulations.

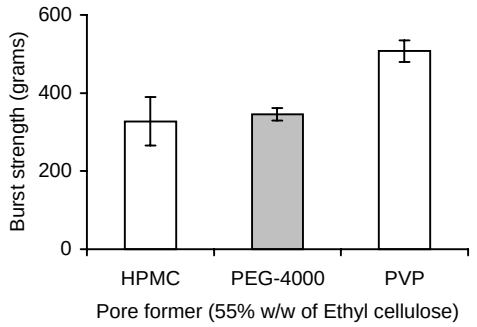


Fig. 8. Burst strength as a function of type of pore former ($n = 6$).

shells (Fig. 8) and this parameter should also be taken into consideration while selecting the pore former.

The drug release and the burst strength were satisfactory with the formulations containing PVP as the pore former. Drug release of this formulation in comparison with the desired profile is shown in Fig. 9. The f_1 and f_2 values were found to be 10.20 and 68.06, respectively taking the desired profile as the reference. This formulation was selected as the "optimized" formulation and used for further evaluation.

3.3. Performance evaluation of the optimized formulation

The optimized formulation was evaluated for various pharmacopoeial and non-pharmacopoeial tests, results of which are listed in Tables 4–6. The ready for powder blend was free flowing as demonstrated by the values of Compressibility Index (5.66) and Hausner Ratio (1.06). Other parameters for the uncoated and coated tablets were also within limits. Exhausted shells, after dissolution, were visually observed for any imperfection or cracks in the coating. There were no visible cracks in the coating and it was found to be intact in all the batches after 24 h of dissolution studies. Exhausted tablets (after 24 h of dissolution studies) were also evaluated for burst strength to assure that the tablets maintain their integrity in GIT and do not lead to dose dumping. The strength of mechanical destructive forces in the GIT of humans and dogs has been reported to be 1.9 N (approximately 190 g) and 3.2 N (approximately 320 g), respectively (Kamba et al., 2000, 2001). In a previous study, it has been reported that osmotic pumps having the burst strength in the range of 500–600 g were intact in the GIT of dogs while those having burst strength of around 200 g were compromised (Jensen et al., 1995). The burst strength

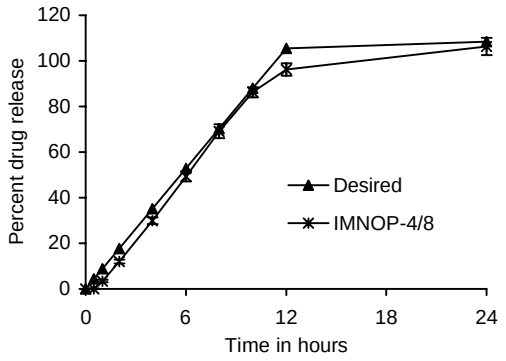


Fig. 9. Release profile of the optimized formulation (IMNOP-4/8) in comparison with the desired profile.

Table 4
Properties of the powder blend of the optimized formulation (IMNOP-4/8)

Parameter	Value
Loss on drying (%)	0.68
Bulk density (g/cm^3)	0.756
Tap density (g/cm^3)	0.801
Compressibility Index (%)	5.66
Hausner Ratio	1.06

Table 5
Evaluation parameters of the optimized core tablets (IMNOP-4/8)

Parameter	Average value	S.D.
Tablet weight (mg, $n = 20$)	301.18	6.62
Thickness (mm, $n = 20$)	3.90	0.032
Diameter (mm, $n = 20$)	9.02	0.01
Hardness (kg/cm^2, $n = 10$)	6.9	1.28
Friability (%)	0.01	–

Table 6
Evaluation parameters of the optimized coated tablets (IMNOP-4/8)

Parameter	Average value	S.D.
Tablet weight (mg, $n = 20$)	334.80	7.83
Thickness (mm, $n = 20$)	4.23	0.033
Diameter (mm, $n = 20$)	9.27	0.016
Hardness (kg/cm^2, $n = 10$)	9.79	0.53
Weight gain (% of the core, w/w)	10.16	–
Content uniformity (%, $n = 5$)	93.47	2.47

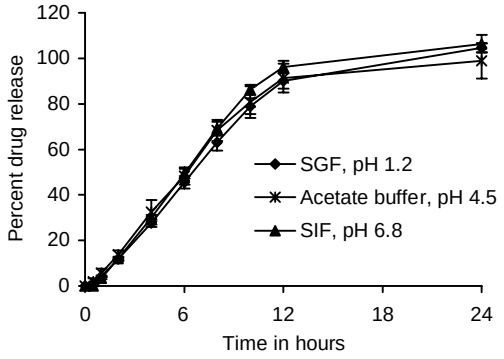


Fig. 10. Effect of pH on IMN release from IMNOP-4/8 formulation.

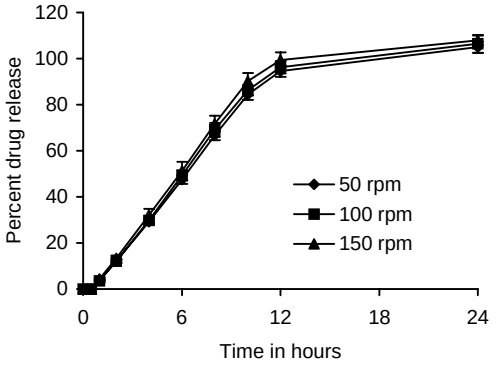


Fig. 11. Effect of agitational intensity of the release media on IMN release from IMNOP-4/8 formulation.

of the exhausted shell was found to be much more than the reported mechanical destructive forces in the GIT of humans, assuring that the formulation would be intact in GIT.

In order to study the effect of pH on drug release, release studies were conducted in media of different pH. Fig. 10 shows release of IMN from IMNOP-4/8 formulation in SGF, pH 1.2; acetate buffer, pH 4.5; and SIF, pH 6.8. As can be seen from the figure, release profile is similar in all the media demonstrating that the developed formulations shows pH-independent release. The f_1 and f_2 values were found to be 6.32 and 75.13 (between SGF, pH 1.2 and acetate buffer, pH 4.5), 7.94 and 67.69 (between SGF, pH 1.2 and SIF, pH 6.8), and 5.92 and 74.78 (between acetate buffer, pH 4.5 and SIF, pH 6.8), respectively.

To study the effect of agitational intensity of the release media, two experiments were conducted. Release studies of the optimized formulation (IMNOP-4/8) were carried out in USP dissolution apparatus type I at varying rotational speed (50, 100, and 150 rpm). It is clearly evident from Fig. 11 that the release of IMN is independent of the agitational intensity. The f_1 and f_2 values were found to be 2.61 and 89.51 (between 100 and 50 rpm), 4.60 and 82.39 (between 100 and 150 rpm), and 7.00 and 73.93 (between 50 and 150 rpm), respectively. To further demonstrate the effect of agitational intensity, release studies of IMNOP-4/8 formulation were carried out in USP-I apparatus (at 100 rpm). To induce stirred and stagnant condition in the same experiment, the stirring was stopped after fixed time intervals. The release rates so obtained were compared with those obtained at 100 rpm (stirred conditions). It can be seen from Fig. 12 that the release rate is similar in both the experiments. Based on the above results, it can be concluded that drug release from *in house* formulations is independent of the agitational intensity of the release media. Therefore, the formulations can be expected to show a release profile, fairly independent of the hydrodynamic conditions of the body.

To study the effect of osmotic pressure, release studies of the optimized formulation (IMNOP-4/8) were conducted in media of different osmotic pressure. Drug release was found to be highly dependent on the external osmotic pressure and IMN release from the formulations decreased with an increase in the osmotic pressure of the release media (Fig. 13). When the release rates obtained were plotted against the osmotic pressure difference across the membrane wall

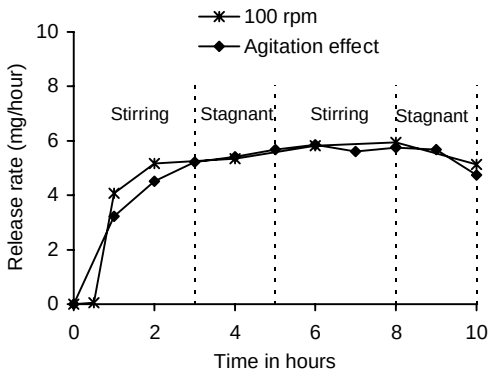


Fig. 12. Effect of agitational intensity and intermittent stirring of the release media on IMN release from IMNOP-4/8 formulation.

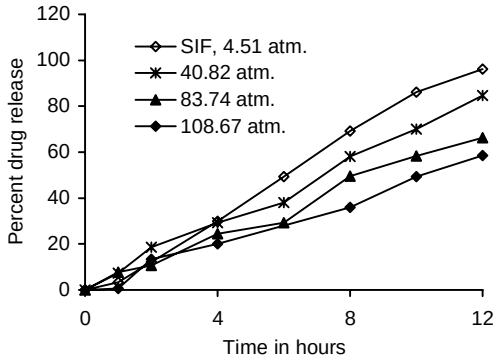


Fig. 13. Effect of osmotic pressure of the release media on IMN release from IMNOP-4/8 formulation.

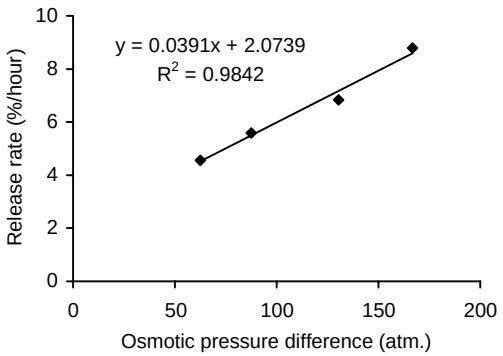


Fig. 14. IMN release from IMNOP-4/8 formulation—effect of osmotic pressure difference across the membrane.

(osmotic pressure of the core formulation was determined to be 171.25 osmol/kg), a linear relationship was obtained (Fig. 14) confirming that osmotic pumping is the major mechanism of drug release from the developed formulations (Liu et al., 1984; Ozturk et al., 1990; Appel and Zentner, 1991; Jensen et al., 1995).

3.4. Kinetics and mechanism of drug release

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of SSR and AIC and best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model (Costa and Lobo, 2001). The dissolution data of IMNOP-4/8 formulation was found to fit well into zero-order kinetics (Table 7) confirming that release from the *in house* formulations to be drug load independent.

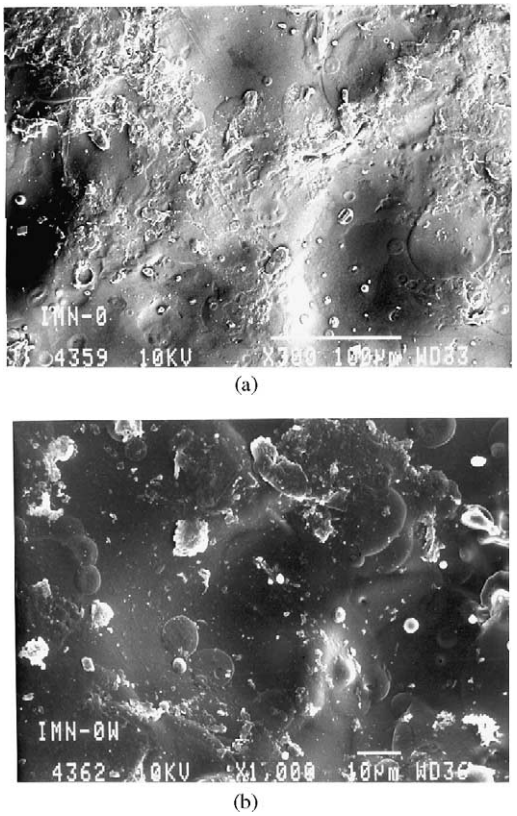
In order to elucidate the changes in the membrane structure, SEM studies were conducted. It was expected that with an increase in the level of pore former, porosity of the membrane should increase because of leaching of pore former from the membrane. This was reflected in the release studies, wherein the release increased with the increase in level of pore former. To further confirm this, the membrane structure was observed before and after dissolution studies (Figs. 15–17). For this study, three *in house* formulations containing 0, 25, and 55% (w/w) of PVP were selected. The membrane structure containing different levels of pore former before dissolution studies is shown in top panel "a" of the Figs. 15–17. In all the cases, the surface appeared smooth and free of any point defects. Before coming in contact with the aqueous environment, there was no significant difference among the membranes containing different levels of pore former (PVP).

In the membrane containing 0% level of pore former, there was no significant difference in the membrane structure before and after dissolution studies (Fig. 15a and b) and there were no pores in the membrane. The surface morphology of the membrane after dissolution studies appeared similar to those

Table 7
Fitting of drug release data of IMNOP-4/8 formulation according to various mathematical models

Model	Parameters used to assess the fit of model[a]						
	R^2	r	Intercept	Slope	k	SSR	AIC
Zero-order	0.9943	0.9971	−4.4840	8.7829	5.2697	44.95	28.64
First-order	0.8967	−0.9469	5.1869	−0.2722	−0.2722	2300.49	56.19
Higuchi	0.9835	0.9917	−42.3770	39.3980	39.3980	129.26	36.03

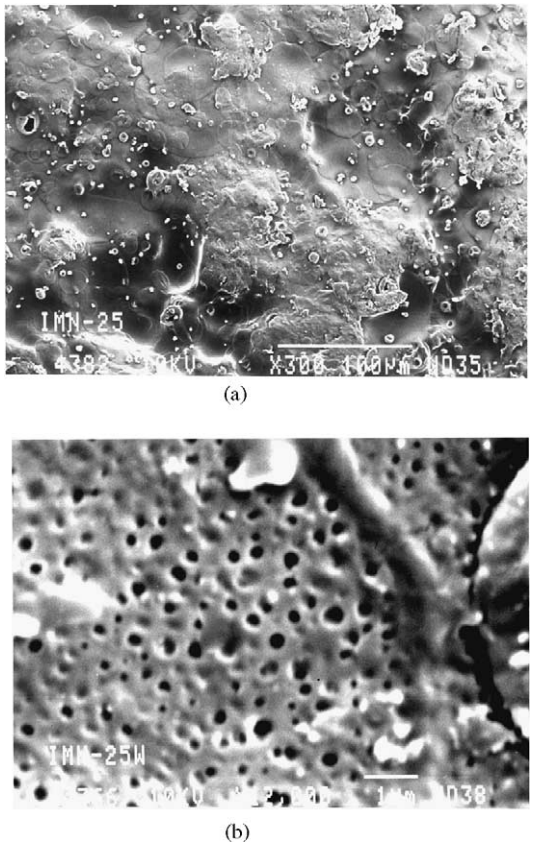
[a] R^2: Goodness-of-fit; r: correlation coefficient; SSR: sum of squared residuals; AIC: Akaike Information Criterion; and k: release rate constant for respective models (k_0 in mg/h, k_1 in h^{-1}, and k_H in $\%/h^{1/2}$ for zero-order, first-order, and Higuchi rate equation, respectively).



(a)

(b)

Fig. 15. SEM micrograph showing the membrane structure of formulation IMNOP-4/4 before (a) and after dissolution studies (b).



(a)

(b)

Fig. 16. SEM micrograph showing the membrane structure of formulation IMNOP-4/6 before (a) and after dissolution studies (b).

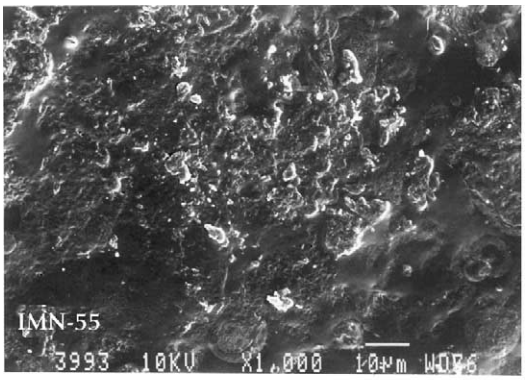
before dissolution studies. It was concluded that the membrane did not develop significant porosity after coming in contact with the aqueous environment. The findings are in agreement with the results of drug release studies (Fig. 2), wherein only 0.59% of the drug was released in 24 h. The membrane structure, after dissolution studies, containing 25% level of PVP is shown in Fig. 16b. SEM micrographs showed formation of pores in the membrane. Membrane that initially contained 55% level of PVP showed considerable porosity after dissolution studies (Fig. 17b). The results are consistent with the drug release studies (Fig. 2), which showed substantial release within 24 h.

3.5. Reproducibility of manufacturing procedure

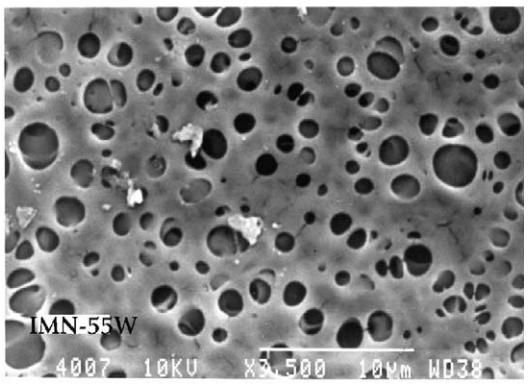
To check the reproducibility of the manufacturing procedure, three batches of the optimized formulations were prepared and coated at different occasions. Release studies were conducted in SIF as per the procedures outlined in earlier sections. It is clearly evident from Fig. 18 that the release profile is similar in all the cases indicating reproducibility of the manufacturing procedure. The f_1 and f_2 values were found to be 3.23 and 86.74 (between batch 1 and 2), 2.03 and 90.34 (between batch 1 and 3), and 4.22 and 79.03 (between batch 2 and 3), respectively.

3.6. Accelerated stability studies

IMNOP-4/8 formulations, packed in strips of 0.04 mm thick aluminum foil laminated with PVC, were stored in ICH certified stability chambers maintained at 40 °C and 75% RH for 3 months. The tablets were withdrawn periodically and evaluated for drug



(a)



(b)

Fig. 17. SEM micrograph showing the membrane structure of formulation IMNOP-4/8 before (a) and after dissolution studies (b).

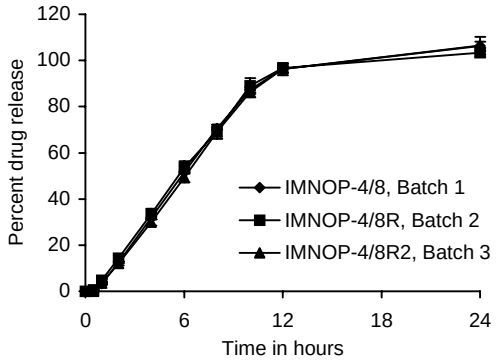


Fig. 18. Reproducibility of the manufacturing procedure—IMN release from three repeat batches.

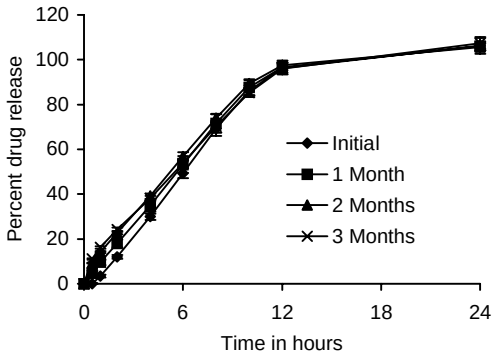


Fig. 19. Dissolution stability of IMNOP-4/8 formulations after 3 months of storage at 40 °C and 75% RH.

content, hardness, burst strength, and release studies. The formulations were found to be stable in terms of drug content and dissolution stability (Fig. 19 and Tables 8 and 9). In all the cases, the burst strength was higher than the reported values of mechanical destructive forces in the GIT (Kamba et al., 2000, 2001), ensuring the formulations to be intact in GIT without any incidence of dose dumping.

3.7. Prediction of in vivo performance

In case of treatment with nitrates, care need to be taken since continuous delivery of the active agent

Table 8
Evaluation of IMNOP-4/8 formulation after 3 months of storage at accelerated stability conditions (40 °C and 75% RH)

Parameter	Initial	1 Month	2 Months	3 Months
Drug content (%)[a]	93.47 ± 2.47	92.56 ± 4.34	96.14 ± 3.01	100.94 ± 4.57
Hardness (kp)[a]	9.79 ± 0.53	7.24 ± 0.66	6.80 ± 0.43	7.46 ± 0.41
Burst strength (g)[a]	507.50 ± 27.46	520.20 ± 134.27	466.37 ± 72.42	463.07 ± 8.50
f_1 value[b]	–	8.60	14.97	14.70
f_2 value[b]	–	66.71	53.74	54.49

[a] Values expressed as average ± S.D.
[b] Initial sample (0 month) was taken as reference to calculate f_1 and f_2 values.

Table 9
Predicted in vivo performance of the developed formulations

Product	Predicted $C_{ss\,max}$ (ng/ml)	% PD	Predicted $AUC_{0-\tau}$ (ng hr/ml)	% PD
Desired[a]	567.62	–	7648.92	–
IMNOP 4/8[b]	569.96	0.41	7733.33	1.10

[a] Predicted from desired zero-order delivery profile (dose = 60 mg, $R^0 = 5.28$ mg/h, and $t_{Del} = 10.48$ h).
[b] Predicted from drug release studies (dose = 60 mg, $R^0 = 5.27$ mg/h, and $t_{Del} = 10.76$ h).

may result in the development of tolerance (Parker and Parker, 1998). It has been mentioned that during the course of nitrate therapy, plasma levels must fall below a specified level for a certain period of time so as to avoid development of tolerance (Jonsson, 1987; Kendall, 1990; Thadani and Bittar, 1992; Parker and Parker, 1998). In case of IMN, it has been suggested that the plasma concentrations should be made to fluctuate during the 24-h period and allowed to fall below a critical level for a certain period of the dosage interval to minimize tolerance development (Nyberg, 1990; Stockis et al., 2002). This level has been estimated to be 300 ng/ml (1500 nmol/l) and postulated as a critical factor in terms of tolerance development (Kendall, 1990; Nyberg, 1990). It is recognized that when trough concentrations of about 100 ng/ml are exceeded, tolerance starts to develop and is fully present when trough level exceeds 300 ng/ml (Neugebauer et al., 1989; Wagner et al., 1990; Jahnchen, 1992).

Method of superposition was used to predict steady-state plasma levels of IMN after administration of a test dose (60 mg) of IMNOP-4/8 formulation (Ritschel, 1989). Since osmotic pumps are reported to exhibit a significant in vitro/in vivo correlation (Swanson et al., 1987; McClelland et al., 1991; Zentner et al., 1991; Jensen et al., 1995), predicted data of steady-state plasma levels from drug release studies can be used for comparison with the desired plasma levels. Prediction of steady-state levels of IMN after administration of a test dose of *in house* formulation showed that plasma levels are above 300 ng/ml but falls to less than 100 ng/ml before administration of the next test dose. Fig. 20 shows predicted steady-state plasma levels after administration of a test dose of IMNOP-4/8 formulation in comparison to the desired levels. The desired steady-state plasma levels

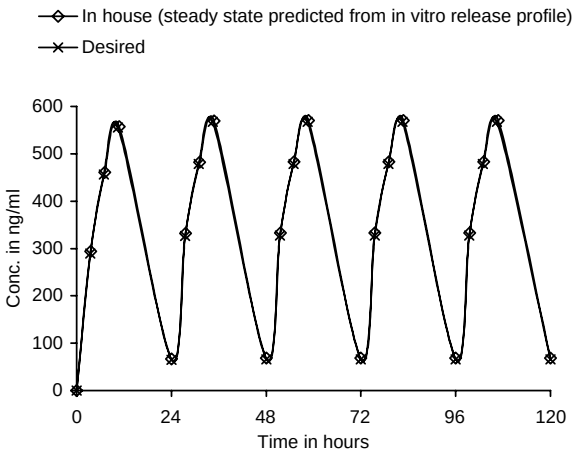


Fig. 20. Predicted steady-state plasma levels of IMN after administration of a test dose of IMNOP-4/8 formulation in comparison with the desired profile.

of IMN were predicted from a theoretically designed zero-order delivery system. It is clearly evident from the figure that the predicted steady-state plasma levels are very close to the desired levels. The predicted $C_{ss\,max}$ and $AUC_{0-\tau}$ after administration of *in house* formulations of IMN, in comparison with the desired ones are listed in Table 9. The % PD of the steady-state parameters of *in house* formulations was calculated taking the data of desired profile as the reference. The absolute % PD was found to be less than 15%, ensuring that the *in house* formulations will produce plasma levels close to the desired ones (Sheskey et al., 1999, 2000). Thus, it can be concluded that the developed formulation (IMNOP-4/8) will produce plasma levels well within the therapeutic range, and at the same time, fall to less than 100 ng/ml before the next dose administration so as to avoid development of tolerance.

4. Conclusions

In the present study, extended release formulations of IMN, based on osmotic technology, were developed. Different formulation variables were studied and optimized to achieve the same. A zero-order delivery strategy, expected to produce plasma levels within the desired range, was employed.

Drug release from the developed formulations was independent of pH and agitational intensity of the

release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. Drug release data from IMN formulations fitted well into zero-order kinetics, indicating the release to be drug load independent. The release was inversely related to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of release. Membranes were found to develop pores/channels after coming in contact with the aqueous environment; the number of pores being dependent on the initial level of pore former in the membrane. Drug release and the burst strength of the exhausted shells were found to be dependent on the level of pore former. Drug release increased and the burst strength decreased with an increase in the level of pore former. The manufacturing procedure was standardized and found to be reproducible. Developed formulations were found to be stable after 3 months of storage at accelerated stability conditions.

From drug release studies, steady-state plasma levels were predicted using the method of superposition. The predicted steady-state levels were within the desired range to show the therapeutic effect and at the same time, below the critical level (100 ng/ml) before the next dosing interval to avoid development of tolerance. Since osmotic pumps are reported to exhibit a good in vitro/in vivo correlation, based on in vivo performance prediction, the developed formulations can be expected to perform similar in vivo.

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