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Design and evaluation of osmotic pump tablets of naproxen sodium

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Osmotic pump tablets (OPTs) deliver a constant, predetermined amount of drug in solution form over a fixed span of time, independent of external environmental conditions. OPTs of naxopren sodium (NPS) were made and evaluated with the principal aim of limiting the drug's frequently experienced gastrointestinal side effects, by preventing the undissolved drug from coming in to contact with the gastric mucosa. OPTs with and without the osmotic driving agent, sodium chloride (SCL), with different membrane thicknesses, and with and without an orifice were designed. *In vitro* release profiles of the OPTs, when compared to a conventional marketed tablet (Xenobid® 275), were highly controlled and exhibited an almost perfect zero-order release pattern. The magnitudes of lag times and average release rates were found to depend on the amount of SCL present in the formulation which decreased the drug's solubility within the system. The release rates were found to be independent of stirring rate and decreased with increasing membrane thickness. Release profiles of the OPTs with and without an orifice were found to be comparable.

1. Introduction

Oral ingestion is one of the most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects [1]. Naproxen sodium (NPS), one of the popular non-steroidal antiinflammatory drugs, is widely used in the treatment of rheumatoid arthritis and other musculoskeletal disorders. Though NPS is effective in the management of these disorders when taken in a standard formulation of 275 mg twice a day, patient compliance can often be enhanced if the dosage schedule is decreased to once a day [2]. Moreover, when given orally in conventional tablets, NPS forms crystals that coat the digestive mucous membrane because of its low solubility in acid media [3]. These crystals dissolve slowly, irritating and damaging the stomach walls and leading to formation of ulcers during prolonged treatment. Studies show that this can be limited by preventing the undissolved drug from coming in contact with the gastric mucosa [4]. Development of an osmotically controlled release dosage form, which delivers the drug in solution form, has been one way of preventing the undissolved drug from coming into contact with the gastric mucosa [5, 6].

Thus, in the present study osmotic pump tablets (OPTs) of NPS were made and evaluated so as to deliver a constant, predetermined amount of the drug in solution form over a fixed span of time independent of external environmental conditions. This formulation is expected to be highly beneficial as it not only reduces the frequency of drug administration but also lessens the gastrointestinal (GI) side effects significantly by exposing the GI mucosae to comparatively lesser amounts of the drug at one time as compared to other conventional formulations.

2. Investigations, results and discussion

Using the pharmacokinetic parameters of NPS [7], the amount of drug required, the required zero-order delivery rate and the dosage interval for the proposed osmotic delivery system were estimated to be 400 mg, 32.76 mg/h and 12 h, respectively. To achieve the objective, OPTs of NPS were prepared with different formulation variables and optimized in terms of physical dimensions of the system, membrane thickness, orifice diameter and solubility of the drug within the system.

Specifications for the various designs of OPT are shown in Table 1. The thickness of the system (an important attribute, as considerable variation in it can ultimately alter the release profile by changing the surface area, volume and other dimensional characteristics of the device) was controlled carefully from batch to batch within an acceptable $\pm 3\%$ variation from a predetermined value.

To study the effect of membrane thickness on the kinetics of drug delivery, OPTs with different membrane thicknesses, viz.- 20 μm (batch I), 30 μm (batch II) and 40 μm (batch III), each with 1.0 mm orifice diameter were prepared and evaluated *in vitro*. The results are shown in Fig. 1. It was observed that a thicker coating membrane (i.e. 40 μm) provided more sustained and linear drug release profile as compared to a thinner coating membrane. Hence, the membrane thickness of 40 μm was used in subsequent batches.

Release profiles of different batches of OPTs, along with that of Xenobid®, are compared in Fig. 2. In contrast to the rapid and uncontrolled release from Xenobid, release of NPS from all the OPTs exhibited a zero-order controlled release profile with a short initial lag period ranging from 0.5 to 1.0 h. This lag period may be attributed to the time taken by the system to hydrate and to solubilize the contents of the formulation core before generating sufficient osmotic pressure to start the zero-order release. Lag times, calculated from the x-intercept when the linear portion of the release curve was extrapolated to zero percent NPS release, along with the time exponent 'n' according to the modified Korsmeyer equation [8] $Q(t) = kt^n$ and other release characteristics, such as average release rate and cumulative percent release at 8 h, for different batches are listed in Table 2 for comparison.

The formulation containing NPS alone without any osmotic agent (batch V) showed a short lag time (0.13 h) and quite fast release (72% in 8 h). When 10% w/w (relative to NPS) of sodium chloride (SCL) was added to the formulation as an osmotic agent (batch III), the lag time was increased to 0.54 h and the average zero-order release rate was decreased. Further increase in SCL content to 30% w/w in batch VI and 50% in batch VII resulted in further prolongation of drug release with a concomitant increase in lag time and a corresponding fall in the average release rate.

To explain the effects of SCL on the release profiles of NPS from the OPTs, we determined the equilibrium solu-

Table 1: Specifications for different batches of OPTs [Mean (S.D) (n = 10)]

S. No.	Specification	Batch No. of formulation						
		I	II	III	IV	V	VI	VII
1.	OPT weight (g)	0.7274 (0.0182)	0.7289 (0.0162)	0.7314 (0.0193)	0.7314 (0.0193)	0.6790 (0.0215)	0.7139 (0.0121)	0.6867 (0.0325)
2.	Thickness (mm)	5.2029 (0.1064)	5.2076 (0.1121)	5.2106 (0.1146)	5.2106 (0.1146)	5.5350 (0.1647)	5.4800 (0.0363)	5.2860 (0.1258)
3.	Diameter (mm)	12.7521 (0.0154)	12.7356 (0.0125)	12.7421 (0.0164)	12.7421 (0.0164)	12.7714 (0.0324)	12.7017 (0.0194)	12.6914 (0.0177)
4.	Drug content (%)	96.82 (1.57)	95.37 (1.73)	94.26 (2.46)	94.26 (2.46)	95.28 (2.52)	98.89 (1.28)	91.53 (3.28)
5.	Surface area* (cm^2)	3.8648	3.8245	3.9954	3.9954	3.8648	3.8180	3.8052
6.	Volume* (cm^3)	0.5657	0.5568	0.5557	0.5557	0.5485	0.5360	0.5243
7.	Osmotic pressure difference** (atm)	72.462	71.869	72.127	72.127	61.276	195.332	311.273

*Calculated from geometry of the device
** Calculated using the equation [14] $\pi = \frac{\nu C_s RT}{M}$ where π = osmotic pressure difference across the membrane at saturation, ν = number of ions into which a molecule ionizes, C_s = concentration of the drug or osmogen at saturation, mg/ml, R = universal gas constant, 0.0821 Lit. atm./mol/deg., T = absolute temperature, 310 °K, M = molecular weight of the drug or osmogen

bility of NPS in distilled water in the presence of different concentrations of SCL at 37 °C. The solubility of NPS, as shown in Fig. 3, decreased sharply with increased SCL concentration, probably due to the common ion effect. This decreased solubility was considered to be responsible for the release profiles (Fig. 2) of OPTs which are in agreement with the theoretical equation proposed by Theeuwes [9], to represent the release rate of drugs from osmotic pump devices

$$dm/dt = (AS/h)\, Lp\sigma\Delta\pi \qquad (1)$$

In Eq. (1), dm/dt is the release rate, A is the surface area of the film coated membrane, h is the membrane thickness, Lpσ is the fluid permeability of the membrane (1.45×10^{-6} cm^2/h atm. for the cellulose acetate membrane [10]), $\Delta\pi$ is the osmotic pressure difference across the membrane at saturation and S is the drug solubility.

The formulation without SCL released NPS at a relatively high average release rate of 34.13 mg/h because of the comparatively high solubility of the drug in this formulation (batch V). As the SCL concentration in the formulation increased, the solubility of NPS decreased steeply with a consequent reduction in average release rate (Eq. 1) and in the percentage of the total drug released in 8 h (Table 2), thereby prolonging the constant release of NPS from such OPTs containing SCL.

To study the effect of agitation intensity, a release study of batch (III) OPT was performed with both static and stirred (100 rpm) dissolution medium (distilled water). The results shown in Fig. 4 indicated no significant ($p > 0.01$) difference in either the rate or the extent of drug release.

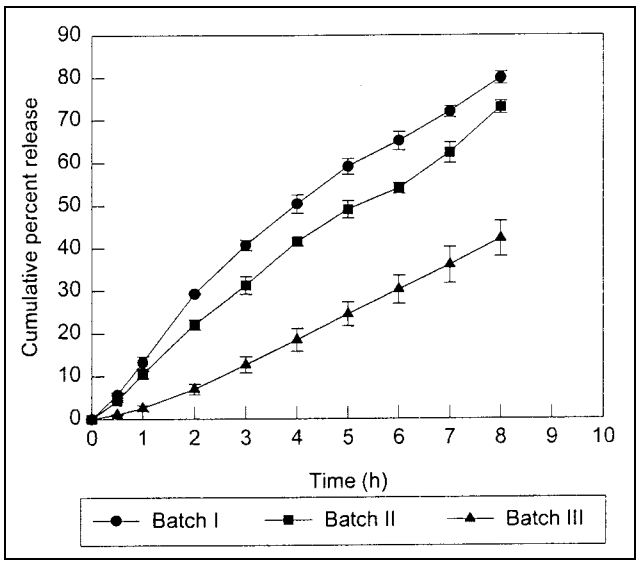

Fig. 1: Comparative release profiles of NPS from OPTs with different membrane thicknesses in distilled water. Bars represent S.D. (n = 3)

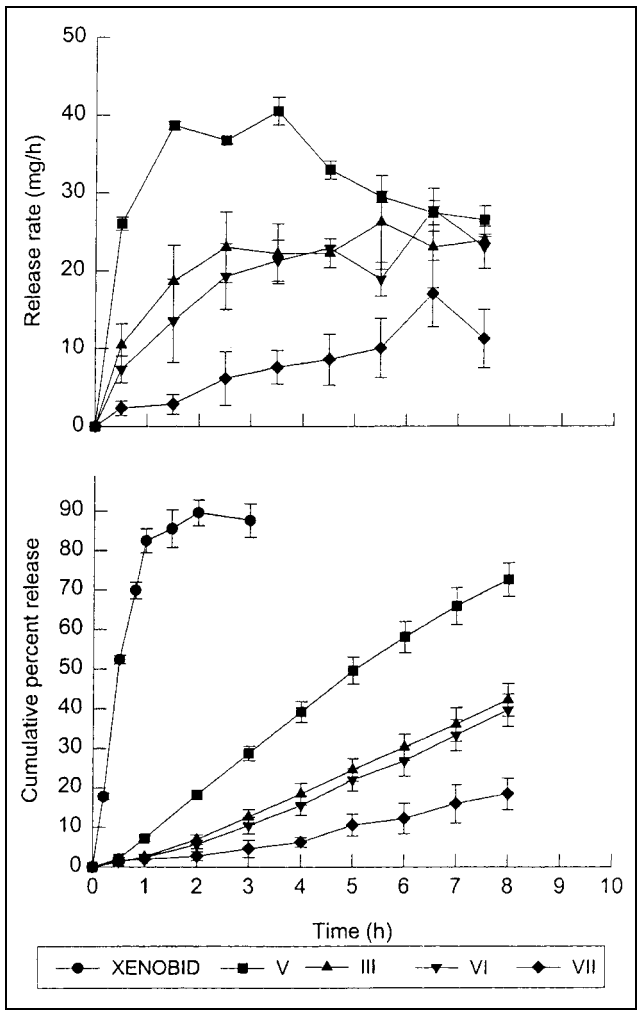

Fig. 2: Comparative release rate profiles of NPS from different batches of OPTs and Xenobid in distilles water. Bars represent S.D. (n = 3)

Table 2: Comparison of release characteristics and the time exponent 'n' (according to the equation $Q(t) = k.t^n$), of different batches of OPTs

Batch No.	Average (n = 3) Lag time (h)	Average (n = 3) release rate (mg/h)	Variance estimate[a] S^2	Mean CPR[b] ± SD at 8 h (%)	Time exponent n	Coefficient of determination r^2
I	zero	37.69	82.4887	79.91 ± 1.46	0.5511	0.9946
II	zero	34.22	39.2861	72.98 ± 1.52	0.6822	0.9928
III	0.84	23.00	0.0165	42.15 ± 4.12	0.9943	0.9999
IV	0.94	21.01	0.5241	36.19 ± 3.26	0.9528	0.9982
V	0.13	34.13	2.8530	72.52 ± 4.24	1.1614	0.9912
VI	1.13	22.68	0.4330	39.56 ± 3.26	0.9452	0.9954
VII	1.36	9.57	0.9497	18.48 ± 9.96	0.8331	0.9637

[a] The variance, as computed here, is an estimate of error in line fitting which is due to the fact that a straight line might not be an accurate representation of the data where, $S^2 = \frac{\left[\Sigma\{Y - (a + bx)\}^2\right]}{N - 2}$
A high value of variance estimate denotes considerable deviation of the release profile from linearity
[b] CPR – Cumulative percent release

In order to simulate complete blocking of the delivery port (orifice), the release of NPS from coated tablets without an orifice (batch IV) was studied in distilled water [11]. It was interesting to observe that during the release study the volume of the coated tablet (system without delivery orifice) was increased and the shape was changed, whereas the OPT with an orifice (batch III) did not change in shape and volume. The drug release profiles shown in Fig. 5 exhibited a non-significant ($p > 0.01$) difference in the rate and extent of drug release from the two batches and drug release followed zero-order kinetics. To explain this, we believe that continuous water influx into the system produced an increase in the volume of the drug solution inside the coated tablet (without orifice) and this led to an increase in hydrostatic and osmotic pressure inside the tablet. The pressure so generated caused expansion and/or weakening of the membrane which in turn, led to the formation of pore(s) in the membrane or increased the size of the existing micropores, thereby delivering the contents through an osmotic delivery mechanism.

This clearly indicates that even in case of accidental blockage of the orifice of the OPT, it is likely that there will be neither dose dumping nor failure of drug delivery and drug release may well still follow a zero-order release pattern.

To further prove our proposition that the delivery of drug from the devices even without an orifice is also osmotically driven, we performed release studies on batch IV OPT (without orifice) at different agitation intensities and in dissolution media of differing osmotic pressures. The results shown in Fig. 6 indicated that the rate and extent of NPS release was independent of the hydrodynamic conditions of the environment but decreased with increased osmotic pressure of the external dissolution medium, as predicted theoretically from Eq. 1, proving that there is also an osmotically controlled mechanism for the release of drug from devices without an orifice.

Based on the findings of the present investigation it was concluded that the desired environmentally independent rate of NPS delivery from OPT can be achieved by opti-

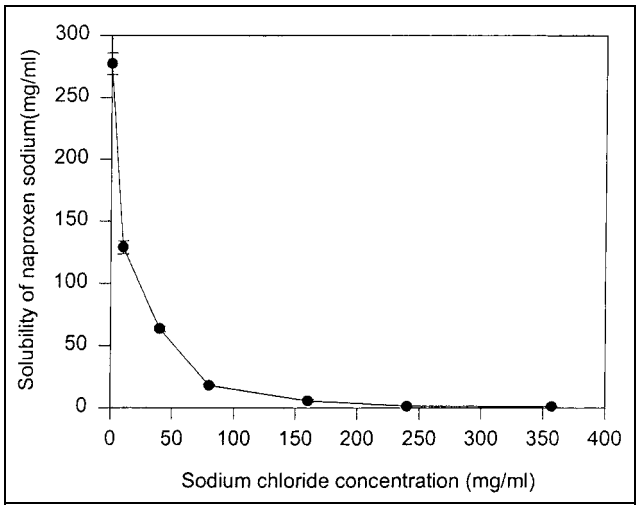

Fig. 3: Solubility of naproxen sodium in different concentrations of sodium chloride. Bars represent S.D. (n = 3)

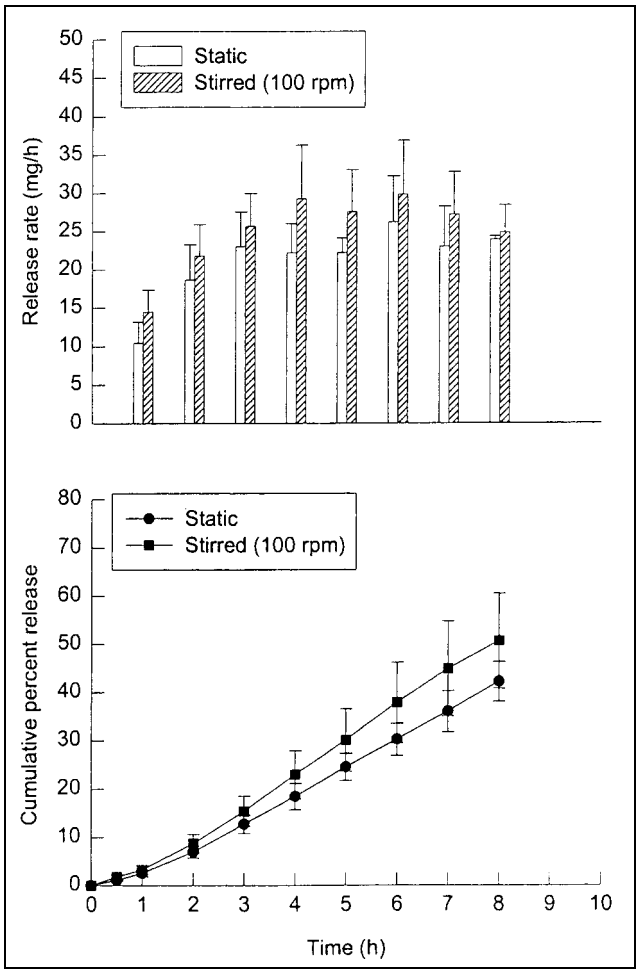

Fig. 4: Effect of agitation intensity on release rate profiles of NPS from batch III OPT in distilled water. Bars represent S.D. (n = 3)

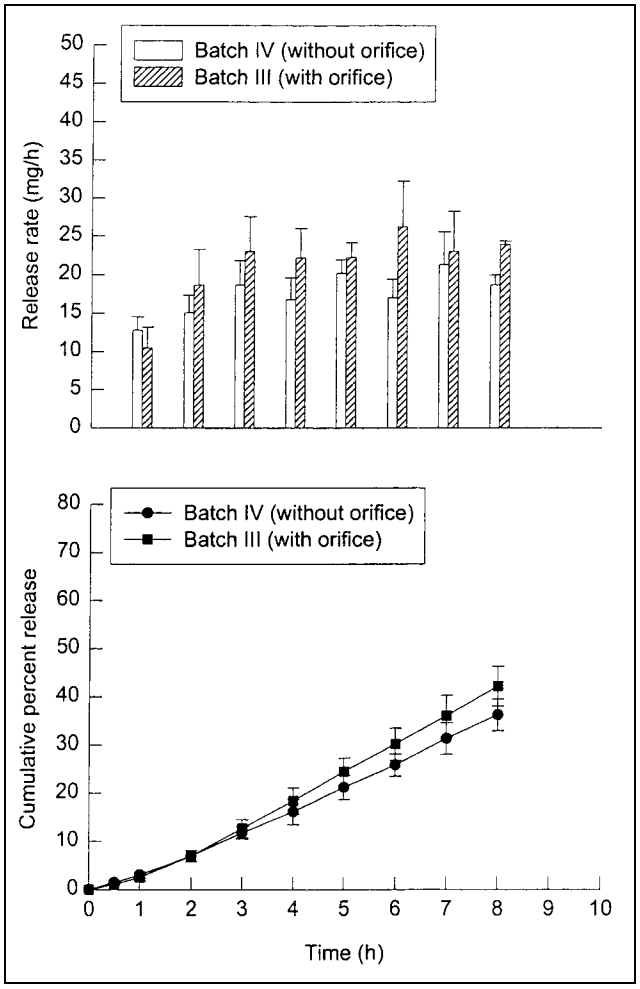

Fig. 5: Comparative release rate profiles of NPS from OPTs with (III) and without (VI) orifice in distilled water. Bars represent S.D. (n = 3)

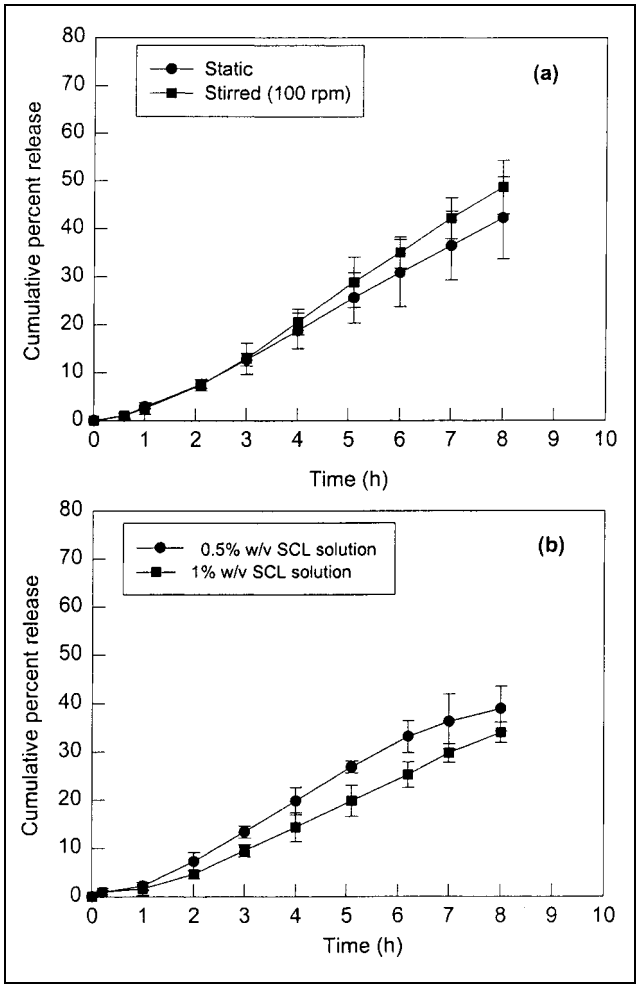

Fig. 6: Effect of (a) agitation intensity and (b) external osmotic pressure on release profile of NPS from batch IV OPT. Bars represent S.D. (n = 3)

mizing the coating of OPT to the correct thickness and by adjusting the solubility of NPS within the system by altering the concentration of SCL in the core tablet. Therapeutic advantages of the formulation can be demonstrated more effectively through *in vivo* studies in appropriate animal models and/or human subjects.

3. Experimental

3.1. Materials

NPS was a gift from Recon Laboratories Ltd. Bangalore, India. Cellulose acetate, 39.8% acetylation (Eastmen, New Delhi, India), microcrystalline cellulose (MCC), polyvinyl pyrrolidone (PVP) (CDH Mumbai, India), and SCL (Qualigens, Mumbai, India), were used. All other chemicals used

Table 3: Formulation variables for different batches of OPTs designed

S. No.	Items	Batch No. of OPTs						
		I	II	III	IV	V	VI	VII
1.	Ingredients (mg/tablet)							
	NPS	400	400	400	400	400	400	400
	Sodium chloride	40	40	40	40	–	120	200
	MCC	190	190	190	190	230	110	30
	SLS	10	10	10	10	10	10	10
	PVP	50	50	50	50	50	50	50
	Talc	4	4	4	4	4	4	4
	Magnesium stearate	4	4	4	4	4	4	4
2.	Total weight of core tablet (mg/tablet)	698	698	698	698	698	698	698
3.	Coat weight* (mg ± SD)	6.0 ± 0.5	7.5 ± 0.5	10.0 ± 0.5	10.0 ± 0.5	10.0 ± 0.5	10.0 ± 0.5	10.0 ± 0.4
4.	Coat thickness* (μm ± SD)	20 ± 5	30 ± 5	40 ± 5	40 ± 5	40 ± 5	40 ± 4	40 ± 5
5.	Orifice diameter* (mm ± SD)	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.1	0.0	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.1

* Mean of 10 determinations
MCC – Microcrystalline cellulose
SLS – Sodium lauryl sulfate
PVP – Polyvinyl pyrrolidone

were of analytical grade and used as received. Dissolution rate test apparatus (Decibel Instruments, Chandigarh, India), and a UV Spectrophotometer (JASCO, Model 7800, Tokyo, Japan) were also used in the study.

3.2. Equilibrium solubility [12]

Solubility of NPS in the presence of different concentrations of SCL was determined by adding excess NPS to solutions of various concentrations of SCL in closed containers at 37 °C. Excess amount of drug was added to ensure saturation and the solutions were equilibrated for 24 h at 37 °C. The saturated solutions were filtered at 37 °C through preheated 0.2 μm millipore filters attached to a syringe and their concentrations determined by UV spectrophotometer at 317 nm after suitable dilution.

3.3. Preparation of core tablets

Accurately weighed quantities of each ingredient (Table 3) were passed through a no. 85 sieve, blended homogeneously and granulated using a 15% w/v aqueous solution of PVP, dried, mixed with talc and magnesium stearate and compressed on a single station tablet press (Manesty, England) equipped with 12 mm standard deep concave punches. The compression force was adjusted to provide tablets with hardness of 7–8 kg/cm^2 on a Monsanto tablet hardness tester.

3.4. Preparation of osmotic pump tablets

The OPTs were prepared by coating the core tablet with 2% w/v cellulose acetate (CA) solution in an acetone-isopropyl alcohol (9 : 1) mixture containing castor oil (20% w/w of total solid CA) as plasticizer, using a conventional laboratory model stainless steel, 10 cm pear-shaped, baffled coating pan (Scientific Instruments, New Delhi, India) and making an appropriate orifice through the membrane by microdrill [13] on one side of the tablet. The coat weight and thus the thickness was controlled by the volume of coating solution consumed in the coating process.

3.5. Evaluation of formulations

The coated tablets were evaluated by visual inspection of the film smoothness, uniformity of coating, edge coverage, luster, and tablet to tablet uniformity. Thickness and diameter of tablets were recorded before and after coating with a standard screw gauge.

3.5.1. Coat weight and thickness

The coat weight and thickness were determined from depleted devices after careful washing and drying [6]. Coat thickness was measured with the help of a screw gauge and weight with an analytical balance.

3.5.2. Orifice diameter

Average orifice diameter of an individual OPT was determined microscopically using a precalibrated ocular micrometer [6].

3.5.3. Drug content

NPS content of the OPTs was determined from a mixed powder sample of 20 tablets in each batch after dissolving in distilled water, and analysing spectrophotometrically at 317 nm.

3.5.4. In vitro release studies

Various OPTs designs were evaluated, in triplicate, for their *in vitro* drug release characteristics in the USP XXI dissolution apparatus 2 at 37 ± 0.1 °C and 50 rpm in distilled water (900 ml) by dropping a tablet into the dissolution medium at time zero and strictly following the standard guidelines for dissolution testing. Drug release from a conventional marketed tablet (Xenobid 275, Rallis India Ltd., Mumbai, Batch No. 2000/71) was studied for 3 h and the release profiles were compared with those of fabricated OPTs. To study the effect of external osmotic pressure on drug release, release studies were performed in distilled water containing 0.5% or 1% w/v SCL. Withdrawn samples were analyzed using an UV spectrophotometer at 317 nm after suitable dilution.

To study the effect of agitation intensity, drug release studies were performed at a relatively high agitation intensity (100 rpm) and under static conditions using the USP dissolution apparatus in distilled water in a similar way to that as discussed in 3.5.4. Under static conditions samples were taken at different times after uniform mixing of the medium.

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