Oral Push-Pull Osmotic Pumps of Pentazocine Hydrochloride: Development and Evaluation

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The present study was aimed to formulate and evaluate oral osmotic pumps of pentazocine HCl that are expected to deliver the drug as solution for prolonged period of time with reduced frequency of drug administration and reduced side effects. Push-Pull osmotic pumps of pentazocine HCl were prepared using different formulation variables like diameter of pores, presence of surfactant in formulation core, addition of osmopolymer pectin and presence/absence of water-soluble polymer (carboxymethylcellulose sodium). Fabricated osmotic pumps were evaluated for weight variation, coating thickness, pore diameter, drug content and in vitro release studies. Release rates were found to be independent of size of pores, agitation intensity, and pH of the release medium. The presence of surfactant, water-soluble polymer and osmopolymer (pectin) affected the drug release significantly. Almost all the osmotic pumps gave controlled and prolonged drug release profiles beyond 2 h of lag phase.

Development of an ideal perorally administered drug delivery system providing constant release of drug has been the focus of many researches, mainly with an objective to provide constant drug delivery during passage through the gastrointestinal tract (GIT), irrespective of variations in pH, surface tension, viscosity as well as motility of the GIT[1]. Osmotically controlled drug delivery is one of such approaches[2], and drug delivery from this system is not influenced by physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form[3]. Pentazocine (PZ), one of the opioid analgesic drugs, is widely used in the treatment of chronic and labour pain. Usual adult dose of PZ is 30-50 mg in three to four divided doses, and elimination half-life is approximately 2 h only[4]. In our earlier investigations[5-7], we have made efforts to develop different types of controlled and prolonged release formulations of PZ. In this study, we have made an effort to develop an osmotically controlled release dosage form of Pentazocine HCl (PZH), which would deliver the drug as solution for prolonged period of time. The developed formulation is expected to provide reduced frequency of dose administration, improvement in patient compliance, and reduction in side effects in comparison to other conventional formulations[8-10].

PZH was gift sample from Ranbaxy Laboratories, Gurgaon. Carboxymethylcellulose sodium (SCMC, high viscosity and low viscosity grades, Central Drug House, New Delhi); Cellulose acetate (CA, 39.8% acetylation, Eastman, New Delhi); Pectin (GS Chemical Industries, Mumbai) were used as received. All other chemicals used were of analytical grade and were used as received. Push-Pull osmotic pumps (PPOP) of PZH were fabricated as bi-layered convex tablets. The upper layer tablet was first prepared as follows. Accurately weighed quantities of ingredients (Table 1) were passed through a sieve No. 85, blended homogeneously and granulated using ethanolic solution of PVP, dried, mixed with sodiumlauryl sulphate, talc and magnesium stearate and compressed on single station tablet press (Manesty E2, England) equipped with 11 mm concave punches. The compression force was adjusted to provide tablet hardness of 6-7 kg/cm^2 on a Monsanto tablet hardness tester. For lower layer tablet, ingredients were blended after sieving (sieve No. 85) and granulated with PVP solution similarly as for upper layer tablet, compressed lightly. Then upper layer tablet was placed over slightly compressed lower layer tablet in the die and finally compressed to get hardness 8-9 kg/cm^2 on Monsanto hardness tester. Coating solution [Cellulose acetate 2% w/v dissolved in acetone using 10% w/w (of CA) castor oil as plasticizer] was used for semi-permeable coatings. Coating operation was performed on a conventional laboratory model stainless steel made, 10 cm pear-shaped, baffled coating pan. The inlet air temperature of 40-45°C and the manual coating procedure was used based on intermittent spraying and drying techniques[9]. An

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appropriate pore was drilled only on the face of the upper layer tablet through the membrane by microdrill, as reported earlier [9].

PZH content of the osmotic pumps was determined from a powder sample of 20 tablets after dissolving in distilled water and analysing spectrophotometrically at 278 nm[5]. Various fabricated osmotic pumps were evaluated in triplicate for their *in vitro* drug release characteristics on the USP XXIV dissolution apparatus 2 containing distilled water as release medium maintained at 37±0.1°C and 50 rpm of stirring. Periodic withdrawn samples were analyzed on UV Spectrophotometer at 278 nm after suitable dilution. To study the effect of agitation intensity, the drug release studies were performed at relatively high agitation intensity (100 rpm), medium intensity (50 rpm) and also under static conditions. Some of the studies were also conducted in release mediums of 0.1N Hydrochloric acid (HCl) (pH 1.2) and of pH 6.8 and pH 7.4 phosphate buffers.

The osmotic pumps were prepared with different formulation variables (Table 1) and optimized in terms of physical dimensions as membrane thickness and pore diameter. All the types of osmotic pumps contained microcrystalline cellulose as a bulk excipient, PVP as a binder, and sodium chloride as one of the osmogen to provide sufficient osmotic pressure inside the drug core. Talc and Magnesium stearate were used as glidant and lubricant respectively. Pectin is a non-toxic water-soluble polymer, derived from citrus peel or apple pomace. It can be used in sustained release as well as matrix tablet formulations[11], and it is reported to have osmogen properties also[12]. So pectin was selected as an osmopolymer in PPOPs (B1, B2).

All osmotic pumps prepared have shown a lag period of 2 h (data not shown) that was required for proper imbibition of formulation core with the release medium. The drug release from PPOPs containing SLS (A1, A2) were significantly higher ($P<0.05$) than batches without SLS (B1, B2) and is attributed to more wetting of drug core due to presence of SLS in A1 and A2. Batches B1 and B2 containing osmopolymer pectin in upper and lower layers exhibited prolonged drug release (Table 1) than batches A1 and A2. Pore size did not show much

TABLE 1: FORMULAE, PHYSICAL PARAMETERS AND *IN VITRO* DRUG RELEASE DATA FOR DIFFERENT PUSH PULL OSMOTIC PUMPS

Ingredients (each in mg)	A1	A2	B1	B2
Upper layer tablet				
Pentazocine HCl	50	50	50	50
Sodium chloride	100	100	100	100
SodiumCMC (low viscosity)	-	25	-	-
SLS	20	20	-	-
MCC	150	150	150	150
Pectin	-	-	20	20
PVP	30	30	30	30
Talc	2	2	2	2
Magnesium stearate	2	2	2	2
Lower layer tablet				
SodiumCMC(high viscosity)	50	25	-	-
Sodium chloride	50	50	50	50
Pectin	-	-	50	50
MCC	100	100	100	100
PVP	30	30	30	30
Talc	2	2	2	2
Magnesium stearate	2	2	2	2
Physical parameters				
Nature of coating membrane	SP	SP	SP	SP
Pore diameter, mm	0.5	0.5	0.5	0.7
Number of pores	one	one	one	one
Coating thickness, mm	31.6±0.2	31.6±0.4	31.6±0.2	31.6±0.3
Surface area, cm^2	3.28±0.12	3.26±0.14	3.30±0.12	3.30±0.15
PPOP weight, mg	600±15	602±20	595±14	589±12
Drug content, %	98.8±2.5	97.5±1.1	96.9±2.1	97.9±1.8
***In vitro* drug release**				
Cumulative % drug release at 8 h	54.32±0.65	61.00±1.03	36.0±0.64	37.0±1.84

SP – semipermeable membrane; - not present; ± values are S.D.

difference in *in vitro* drug release batch B1-0.5 mm pore size, batch B2-0.7 mm pore size (Table 1). This finding is in agreement with similar claims of Theeuwes[13] and Ramadan and Tawashi[14], who had earlier reported drug delivery rate being independent of pore sizes within predictable limits and low agitation speed. Osmotic pumps essentially contain an active agent having suitable osmotic pressure, contained into a tablet coated with a semi-permeable membrane, usually of cellulose acetate. A small orifice is drilled through the coating by using laser or high-speed mechanical drill. In fact, this system represents a coated tablet with an aperture. When exposed to an aqueous environment, the drug and/or the osmotic core imbibes water through the semi-permeable coating, resulting in formation of a saturated aqueous drug solution within the device. The membranes are non-extensible, and increase in volume due to imbibition of water or presence of swellable polymer in the lower layer tablet raises inner hydrostatic pressure, eventually leading to flow of saturated solution of active agent out of the device through small orifice present in upper layer tablet[13]. The presence of water-soluble polymer SCMC could generate hydrodynamic pressure in lower layer tablet, increasing the drug-release rate. Presence of low viscosity grade SCMC in upper layer tablet in addition to presence of high viscosity SCMC in lower layer tablet (PPOP batch A2) gave significantly higher release than high viscosity SCMC present in lower layer only (PPOP batch A1). This might be due to presence of low viscosity grade SCMC in the upper layer of batch A2, leading to generation of more hydrodynamic and osmotic pressure[15,16] as compared to batch A1. This result is in accordance with our earlier investigation[17]. However, the presence of pectin in lower layer in batches B1 and B2, in place of high viscosity grade SCMC, exhibited prolonged drug release and is attributed to lower hydrodynamic pressure provided by pectin than SCMC. *In vitro* release rate profiles of PZ from PPOP batch (A1) under static and stirred (50 and 100 rpm) conditions of release medium (distilled water) indicated insignificant effect ($P>0.01$) of stirring conditions on drug release (data not shown). Osmotic pump A1 was also studied for *in vitro* drug release in 0.1N HCl (pH 1.2) and in phosphate buffers of pH 6.8 and pH 7.4, and the results were compared with drug release in distilled water (pH 6.1). The profiles clearly indicated that pH change had negligible effect ($P>0.01$) on rate and extent of drug release from osmotic pumps (data not shown).

Based on the findings of the present investigation, it was concluded that the desired environmentally independent rate of PZH delivery from oral osmotic pumps could be achieved by incorporating SLS (wetting agent), osmopolymer and optimised amount of polymer like SCMC in upper and/or lower layers. The therapeutic advantages of the formulation can further be demonstrated more effectively through *in vivo* studies in appropriate animal models and/or human subjects.

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