Research Article

FORMULATION AND OPTIMIZATION OF POROUS OSMOTIC PUMP–BASED CONTROLLED RELEASE SYSTEM OF RESIDRONATE SODIUM FOR THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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ABSTRACT

The aim of the current study was to design a porous osmotic pump-based drug delivery system for controlled release of Residronate sodium. The porous osmotic pump contains pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a micro porous structure. The dosage regimen of Residronate sodium is 35-mg tablet once in a week. The drug eliminated in urine (about 50%) is in 24hrs. Hence, Residronate sodium was chosen as a model drug with an aim to develop a controlled release system for a period of 24 hours. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the in vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release. The porous osmotic pump tablet was prepared by wet granulation technique using controlled release polymer hydroxyl propyl methyl cellulose (HPMC) and using different osmogents (mannitol, fructose). The coatings of core tablets were prepared by using CA with PEG400 and using pore forming agent sorbitol. The tablet formulation (F4) containing 100mg of HPMC and 100mg of mannitol with coating solution of CA and sorbitol considered as overall best formulation (with an *in vitro* release of 98.76% and Scanning Electron Microscopy (SEM) analysis with proper pore formation after dissolution). Residronate sodium release was inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver Residronate sodium at a zero-order rate for 24 hours. Short term stability study (at 40±2°C/75±5% RH for three months) on the best formulation indicated that there no significant changes in drug content. IR spectroscopic study indicated that there are no drug excipient interactions.

Keywords: Osmotic system, Residronate sodium (RSD), Osmogent, Cellulose acetate.

INTRODUCTION

In a typical therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than one or twice daily, greatly reduces patient compliance. So in recent year considerable attention has been focused on the development of novel drug delivery system and the main reason for this paradigm shift is relatively low development cost and time required for introducing a novel drug delivery system as compared to a new chemical entity. In the form of novel drug delivery system, an existing drug molecule can get a new life there by increasing its market value competitiveness and patent life among the various novel drug delivery system available in the market, per oral controlled release system hold the major market share because of their obvious advantages of ease of administration and better patient compliance. These products provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule.

Hence Oral controlled release systems continue to be the most popular amongst all the drug delivery systems[1,2]. Because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices over the past 2 decades. A detailed review of various types of osmotic pumps has been done by Santus and Baker[3]. Drug delivery from this system is not influenced by the different 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. Theeuwes introduced the elementary osmotic pump (EOP)[4]. The EOP consists of an osmotic core, with the drug surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice. Various attempts to increase the

permeability of the semipermeable coating have been reported, such as incorporating water-soluble pore-forming additives in the coating. The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media. It was observed that predominantly the drug was released through the pores at a constant rate. It was also observed that most of the core content released through pores at a constant rate, where the mechanism was primarily governed by osmosis with simple diffusion playing a minor role. Osmotic tablets with an asymmetric membrane[5] coating that can achieve high water fluxes have also been described. Residronate sodium is used as the treatment of postmenopausal osteoporosis. Residronate sodium is a white crystalline powder with a molecular weight of 305.11. It is readily soluble in 0.1M sodium hydroxide, phosphate buffer pH 7.4 and sparingly soluble in water. The objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of Residronate sodium. Fructose and Mannitol were used as the osmogent. The tablets were coated with cellulose acetate as the semipermeable membrane containing sorbitol as a pore forming/channeling agent.

MATERIALS AND METHODS

Materials

Residronate sodium was obtained from Dr Reddy's pvt Ltd, India. Mannitol (Pearlitol SD 200, Roquette, France), Lactose (Pharmatose DCL 11, DMV International, Veghel, The Netherlands) and Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol and polyethylene glycol (PEG) 400 were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. All other solvents and reagents used were of analytical grade.

Drug excipient studies

The IR allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the IR study the major peak of RSD were found to 3618, 3348, 3095, 3061, 2359, 1508 cm^{-1}. The major peaks of HPMC was found to at 3260, 2341, 1520 cm^{-1}. In the formulation of osmotic pump (F4) peak at 3261 cm^{-1} was due to presence of the polymer HPMC, peak at 2359 and 1509 cm^{-1} was due to the presence of drug RSD in the formulation. So from the study it can be concluded that the major peaks of drug (2359, 1508 cm^{-1}) remains intact and no interaction was found between the drug and polymer.

Preparation of osmotic pump tablets

The tablets were prepared by wet granulation technique. Accurately weighed quantities of ingredients mentioned in Table-1 were passed through sieve No. 30 and lubricant and glidant were passed through sieve No. 80. All the ingredients except lubricant (magnesium stearate), glidant (talc) were manually blended homogenously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution and granulated through sieve No.30 and dried in a hot air oven at 60°C for sufficient (3-4 hrs). So that the moisture content granules reached to 2-4%. The dried granules were passed through sieve No.30 and blended with talc and magnesium stearate. The homogenous blend was then compressed into round tablets (350 mg each) with standard concave punches (diameter 10 mm) using 27 station rotary compression machine (CMB4D-27 Cadmach, Engg, Ahmedabad, India).

Table 1: Composition of osmotic pump tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
	Mg/tablet						
Residronate sodium	35	35	35	35	35	35	35
Lactose	210	110	110	110	110	110	110
HPMC	100	100	100	100	100	100	100
Mannitol	---	100	---	100	---	100	---
Fructose	---	---	100	---	100	---	100
Magnesium stearate	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3
Total	350	350	350	350	350	350	350

Table 2: Coating composition for Residronate sodium tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
CA	6gm	6gm	6gm	6gm	6gm	6gm	6gm
PEG 400	0	0	0	2gm	2gm	2gm	2gm
Sorbitol	0	0	1.2gm	0	1.2gm	0	1.2gm

N.B- PEG 400 taken as 1ml for coating solution; F6=F4+CA+PEG 400+Sorbitol; F7=F5+CA+PEG 400

Coating of core tablets

Table-2 summarizes the components of coating solution. The coating solution was prepared using mixtures of (CA 6gm+33% of PEG 400 of CA). The CA was passed through sieve No.80 then mixed with 33% of PEG400 and acetone was added quantity sufficient maintaining proper viscosity of solution. The coatings of tablets were performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). Initially tablets were pre heated by passing hot air through the tablet bed and by rotating at a lower speed of 5-8 r.p.m. Coating process was started with rotation speed of 10-12 r.p.m. The spray rate and atomizing air pressure were 4-6 ml/min and 1.75 kg/cm^2 respectively. Inlet and outlet air temperature were 50°C and 40°C respectively. Coated tablets were dried at 50°C for 12 hrs.

Evaluation of granules

Angle of repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan q = h/r$$

Therefore, $q = \tan^{-1} h/r$

Where **q** = angle of repose.

h = height of the cone in cm.

r = radius of the cone base in cm.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas

Bulk density = weight of the powder/bulk volume of the powder

Compressibility index

The compressibility index of the granules was determined

By Carr's compressibility index.

Carr's index % = Dt - Db / Dt ×100

Where, Dt is the tapped density of the granules.

Db is the bulk density of the granules

Evaluation of tablets

Thickness: The thickness of six tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5 % of the standard value was determined.

Hardness: Monsanto hardness tester determined hardness of the tablets. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded

Friability: Friability of tablets was performed in a Roche friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed.

Weight variation test: Uniformity of weight test as described in the IP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation.

Uniformity of drug content: Drug content for RSD tablet was done by the assay method. First the prepared tablet (35mg API) was crushed and added to 100ml of phosphate buffer pH 7.4. After 30 minutes the solution was filtered and diluted up to 250ml which was the stock solution. From the stock solution 2.85ml was withdrawn and diluted up to 50ml getting desired concentration 8µg/ml. From the desired concentration, the drug content of formulations were calculated using calibrated standard curve equation y=0.005x+0.001.

***In vitro* dissolution studies:** *In vitro* dissolution study was performed by using USP Type I Apparatus (Basket type) [Electrolab (ETC-11L) Tablet Dissolution Tester]. The tablet was kept in 900ml of dissolution fluid phosphate buffer pH 7.4 and stirrer rotating with 100 r.p.m and maintaining the temperature 37±0.2°C of dissolution media. 10ml of samples were withdrawn at different time intervals replaced with fresh medium and analyzed in (UV-Visible spectrophotometer ELICO SL 164) at λmax 262nm.

SEM analysis: Coating membrane of formulation obtained before and after complete dissolution of tablets was examined for their porous morphology by SEM (XL-30 ESEMTMP+EDAX, Philips, Eindhoven, The Netherlands). Membranes were dried at 45°C for 12 hrs and stored between sheets of wax paper in a desiccator until examination.

Statistical analysis: Except dissolution all evaluation parameters were expressed as mean ± standard deviation.

Stability studies: Short term stability studies on the above promising formulation (at 40±2°C/75±5% RH for 3 months) have shown no significance changes in physical appearance and drug content.

RESULTS AND DISCUSSION

All the compressible excipient by wet granulation method was prepared using lactose along with mannitol and fructose. This excipient was evaluated for bulk density, tapped density and Carr's index.

Osmotic pump tablets of RSD were prepared by using the above excipient and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index and angle of repose (Table-3) and for post compression parameters such as hardness, weight variation, friability, thickness and drug content uniformity (Table-4).

Table 3: Precompression parameters of RSD formulation

Formulation code	Bulk density (gm/cc)±S.D	Tapped density (gm/cc)±S.D	Angle of repose (degree) ±S.D	Carr's Index (%)±S.D
F1	0.57±0.06	0.64±0.05	26.27±0.98	12.28±0.01
F2	0.58±0.05	0.66±0.01	28.36±0.89	12.12±0.03
F3	0.58±0.03	0.67±0.03	28.42±1.06	13.43±0.02
F4	0.59±0.04	0.69±0.03	25.42±1.03	14.49±0.01
F5	0.63±0.02	0.71±0.02	24.97±0.93	11.26±0.03
F6	0.65±0.03	0.73±0.04	24.73±1.08	10.95±0.05
F7	0.62±0.02	0.71±0.02	24.32±0.92	12.67±0.02

Table 4: Postcompression parameters of formulation.

Formulation code	Hardness (kg/cm^2) ±S.D	% Friability±S.D	%Drug content±S.D	Average wt. of tablets±S.D	Thickness (mm±S.D)
F1	6.9±0.114	0.58±0.01	98.85±0.01	350.2±0.01	5.50±0.28
F2	6.8±0.118	0.88±0.03	97.73±0.42	350.5±0.13	5.50±0.11
F3	6.8±0.152	0.94±0.08	97.60±0.13	350.3±0.21	5.50±0.07
F4	7.1±0.155	0.52±0.01	99.3±0.12	350.3±0.14	5.50±0.12
F5	6.9±0.153	0.67±0.02	98.42±0.25	354.3±0.51	5.45±0.14
F6	7±0.110	0.79±0.06	98.79±0.13	352.6±0.16	5.50±0.10
F7	7.2±0.113	0.85±0.01	98.26±0.22	350.6±0.11	5.50±0.11

The bulk density of pre-compression blends was found to be in the range of 0.57 to 0.65 gm/cc, tapped density in the range of 0.64 to 0.73 gm/cc, the Carr's index values were in the range of 10.95 to 14.49% and angle of repose in the range of 24.32 to 28.42. The hardness of the tablet formulations was found to be in the range of 6.8 to 7.2 kg/cm^2. The friability values were found to be in the range of 0.52 to 0.94%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits. The percent drug content of all the tablets was found to be in the range of 97.60 to 99.3% of the expected RSD content, which was within the acceptable limits. The results are shown in Table-4. The thickness values were found to be in range of 5.45-5.50mm.

Content uniformity

From the content uniformity test by assay method it was found that the percentage of drug content (%D.C) was maximum in F4 formulation (99.3±0.12). Hence it was the best formulation among the various formulations like F1, F2, F3, F5, F6 and F7 (Figure-1).

In vitro dissolution studies

From the *in vitro* drug release study it was found that the percentage of drug release (%D.R) was maximum in F4 formulation giving 98.76% of drug release. Hence it was the best formulation among the various formulations like F1, F2, F3, F5, F6 and F7 (Figure-2).

Figure 1: Comparative study of % D.C of various formulations.

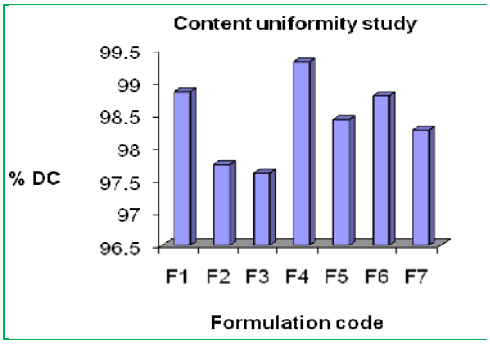
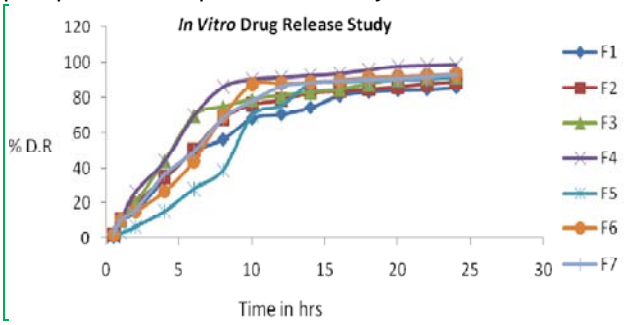
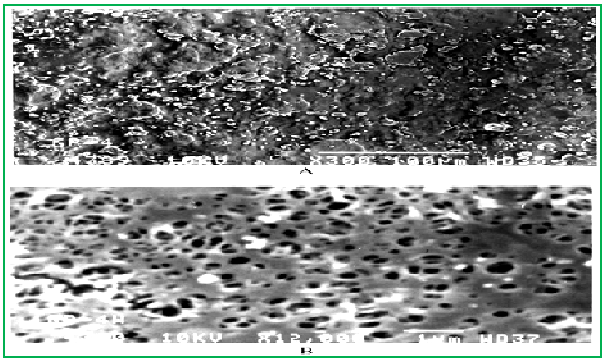


Figure 2: Comparative % of drug release study using phosphate buffer pH 7.4 SEM analysis



SEM analysis

The coating membrane of the osmotic delivery system before and after dissolution was examined or porosity with the help of SEM. Before dissolution fewer pores were found in the coating membrane. But after dissolution comparatively more numbers of pores were found in the membrane might be due to leaching or removal of entrapped drug from the formulation. The porosity nature of the membrane was due to the presence of pore forming agent sorbitol in the formulation (Figure-3).



A-Before Dissolution; B-After 24hr Dissolution

Figure 3: Scanning electron photographs of membrane structures of optimized formulation before and after dissolution

CONCLUSION

A porous osmotic pump based drug delivery system can be designed for controlled release of Residronate sodium using HPMC as controlled release polymer, mannitol as osmogen & sorbitol as porogen. It was evident from the results that rate of drug release can be controlled through osmotic pressure of the core, the level of pore former. From the developed formulations the release of Residronate sodium was best in F4 formulation i.e. osmotic based (*in-vitro* study). The result of SEM studies confined the formation of pores in the membrane after coming into contact with the aqueous environment. From the FTIR study, it was confirmed that the drug & excipients in the formulations were compatible with each other.

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