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Studies in Formulation of Delayed Release Capsules of Doxycycline Hyclate

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Abstract

The objective of the study was to prepare delayed release doxycycline hyclate capsules with suitable blend of doxycycline hyclate-coated pellets (DC pellets) and delayed release pellets (DR pellets). Formulation was optimized on the basis of *in vitro* drug release. DC pellets were prepared to optimize the amount of polyvinyl pyrrolidone and the optimum concentration was found to be 5%. Two batches of DC pellets showed desired release in buffer medium. DR pellets formulation was optimized using polymer and other variables. The blend of DC pellets (75%) and DR pellets (25%) in capsules produced an optimum drug release in acid and buffer media.

Key words: Doxycycline hyclate, Drug coated pellets (DC Pellets), Delayed release pellets (DR pellets)

Introduction

Doxycycline hyclate is one of the most important semi-synthetic tetracycline derivatives with broad spectrum activity and used orally in respiratory tract, gonococci , chlamydia infections and traveller's diarrhoea (AFS Handbook, 2003). Side effects such as gastric irritation, oesophagitis and epigastric distress are observed due to high concentration of the drug in the stomach (Liebowitz *et al.*, 1972 and Collens *et al.*, 1979). Delaying the release of

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the drug might decrease gastric irritation since there would be reduction in gastric localization of the drug. Doxycycline hyclate is well absorbed from stomach (pH 1.6) and duodenum (pH 5.5) (Renolds, J.E.F., 1993). Modifying release of the drug wherein only a part of the drug is allowed to be released in stomach and remaining in the intestine is expected to provide adequate drug plasma level with out gastric distress. Hydroxypropylmethylcellulose phthalate-55 (HPMCP55) is an anionic polymer derived from cellulose. The polymer shows enteric coating properties mainly because it is insoluble in the acid medium.

The objective of the present study was to prepare delayed release capsules of doxycycline hyclate using HPMCP55 as an enteric polymer and to study the effect of variables on the drug release. The delayed release capsule was formulated by blending drug-coated pellets and delayed release pellets.

Materials and Methods

Material

Doxycycline hyclate was obtained from M/s Kaifeng, China. HPMCP55 (Signet Corp., Mumbai), PVP, polyvinyl pyrrolidone K30 (BASF Corp., New Jersy), sodium starch glycolate (Yungzip Chemical Industries, Taiwan) and colloidal silicone dioxide, Aerosil^{R} 200 (Coverlal and Company, Chennai) were used. All other ingredients used throughout the study were of analytical grade and were used as received.

Drug coated pellets (DC pellets)

The composition and results of drug release of doxycycline hyclate-coated nonpareil seed pellets (DC pellets) are shown in Table 1. The amount of binder polyvinyl pyrrolidone (PVPK30) in DCP1 failed to give proper drug loading on nonpareil seed pellets and hence increased in subsequent batches. The composition with respect to inclusion of sodium starch glycolate in DCP3 and DCP4 was selected to adjust drug release from DC pellets in buffer medium. In DCP4 the ratio of drug and nonpareil seeds were varied keeping the composition of the coating solution same as that of DCP3. The coating solution was sprayed continuously over cascading nonpareil seeds (30-36 mesh size) along with doxycycline hyclate powder (previously sized through 100 mesh) loaded in 18 inches diameter coating

pan using 0.5 mm fluid nozzle spray gun. The rpm of the coating pan and the atomizer air pressure were maintained at 35 and 3 to 3.5 kgf/cm^2, respectively. The pellets were coated up to weight gain of 40-45% by weight of nonpareil seeds. The DC pellets were dried at 45-50° C in a tray drier for 4-5 hours.

Table 1. Composition and results drug release for the selection of doxycycline hyclate DC pellets

Formula Code	Composition (%W/W) of solution in isopropyl alcohol				Drug: Non-pareil seed	Drug release (%) in	
	PVPK 30*	SLS*	SSG*	Aerosil		Acid	Buffer
DCP1	3.0	0.1	-	-	2:1	99.5 (1.14)	62.5 (1.43)
DCP2	5.0	0.1	-	-	2:1	99.6 (1.21)	63.6 (1.19)
DCP3	5.0	0.1	0.5	0.05	2:1	98.9 (1.42)	97.6 (0.75)
DCP4	5.0	0.1	0.5	0.05	3:1	99.1 (1.18)	98.1 (1.24)

*-PVPK30 – Polyvinyl pyrrolidone K30, SLS - Sodium lauryl sulphate, SSG – Sodium starch glycolate

Figures in the parentheses represent ±SD, n=3.

Delayed release pellets (DR pellets)

The composition and results of drug release of doxycycline hyclate delayed release pellets (DR pellets) are given in Table 3. The concentration of HPMCP55 specified in Table 2 was developed as an optimum concentration to adjust drug release in acidic medium as per predetermined limits (to be mentioned later). The inclusion of sodium starch glycolate was developed to adjust drug release in buffer medium. The coating solution (Table 3) was sprayed continuously at 5 g/min rate over the DC pellets bed (pre-warmed to 40^0 C) loaded in 18 inches diameter coating pan using 0.5 mm fluid nozzle spray gun. The rpm of the coating pan, the atomizer air pressure and the drying temperature were maintained at 35, 3 to 3.5 kgf/cm^2 and 50 to 55^0 C, respectively. The DC pellets were coated to weight gain of 22±2% by weight of DC pellets with an objective of 18 to 20% by weight HPMCP55 coating over DC pellets and to get uniform thickness of coating.

Table 2. *In vitro* drug release profile of doxycycline hyclate DR pellets made from DCP3 at
various polymer concentrations

S. No.	HPMCP55* concentration (%)	Drug release (%) in	
		Acid medium	Buffer medium
1	5	100.3 (1.12)	70.11 (1.16)
2	10	88.11 (1.32)	74.20 (1.62)
3	15	46.22 (0.98)	69.31 (1.67)
4	20	10.21 (1.43)	60.65 (1.39)

*-HPMCP55-Hydroxypropylmethylcellulose phthalate 55; Figures in the parentheses represent ±SD, n=3.

Table 3. Composition and results drug release for the selection of doxycycline hyclate DR pellets

Formula Code	Composition (%W/W) of solution in mixture of IPA and methylene chloride (30:70)					Drug release (%) in	
	DC pellets	HPMC55	DET*	SSG	Aerosil	Acid	Buffer
DRP1	DCP3	10	2	-	-	26.2 (1.12)	65.7 (1.32)
DRP2	DCP4	10	2	2.5	0.05	11.2 (1.61)	73.9 (1.74)
DRP3	DCP3	10	2	3.0	0.06	12.4 (1.17)	78.2 (1.22)
DRP4	DCP4	10	2	3.0	0.07	10.3 (1.57)	79.7 (1.84)

*- Diethyl phthalate; Figures in the parentheses represent ±SD, n=3.

The blend of doxycycline hyclate delayed release pellets (DR pellets) and DC pellets at the ratio of 75:25 were mixed and the capsule fill weight was adjusted to 270 mg with dummy pellets and blended in coating pan. This blend equivalent to 115 mg doxycycline hyclate (100 mg doxycycline) was filled in capsule size number 2. The formulae of DR capsules are shown in Table 4.

Table 4. Composition of delayed release capsules (blend of DC and DR pellets)

DR capsules	DR pellets (75%)	DC pellets (25%)
DRC1	DRP2	DCP3
DRC2	DRP3	DCP4
DRC3	DRP4	DCP3
DRC4	DRP4	DCP4

Evaluation

The prepared capsules were tested as per standard procedure for weight variation, drug content and *in vitro* drug release characteristics. The pellets were evaluated for *in vitro* drug release. The drug content for doxycycline hyclate was carried out as per USP (US Pharmacopoeia, 2002a) by measuring the absorbance of samples at 345 nm using Unicam (Hedios) UV/Vis spectrophotometer and comparing the content from a calibration curve, prepared with USP doxycycline hyclate RS.

Drug release was studied using USP 24 basket dissolution apparatus (US Pharmacopoeia, 2002b) and method B for drug release studies under two different physiological conditions of acid stage and buffer stage (pH 5.5). Dissolution test was carried out for 20 min using hydrochloric acid (pH 1.2) as dissolution medium at 37±0.5° C and at 50 rpm. Dissolution was also carried out for 30 minutes in buffer medium (pH 5.5) using separate samples that were not subjected to acid medium test. In both cases 5 ml of samples were withdrawn, filtered and drug content in each sample was analysed after suitable dilution by above mentioned spectrophotometer at 345 nm. The actual content in samples was read from a calibration curve, prepared with USP doxycycline hyclate RS. The predetermined drug release USP 24 requirement is in acidic medium (not more than 50%) and in buffer medium (not less than 90%).

Results and Discussion

The results of *in vitro* release of the DC and DR pellets are given in Tables 1 and 2. The optimum concentration of PVP to make DC pellets was found to be 5%. The *in vitro* releases

for DCP1 and DCP2 in buffer medium were found to be very less (62.5% and 63.6% respectively). The inclusion of sodium starch glycolate (0.5%) and aerosil (0.05%) increased the release in buffer medium significantly. Aerosil reduced agglomeration of pellets and produced pellets with glossy surface and thereby good flow properties. The *in vitro* release of DR pellets of the formulation DRP1 in acid was 26.20%. The inclusion of sodium starch glycolate in other formulae of DR pellets (DRP2, DRP3 and DRP4) showed that acid resistance of the film was increased due to its insolubility in acidic pH and thereby release of the drug in acid medium reduced. The higher concentration of sodium starch glycolate in DRP3 and DRP4 did not affect the acid resistance of the film , it did increase the release in buffer medium.

Table 3 shows the influence of HPMCP55 on the delayed release of doxycycline from DR pellets. We found a minimum 15 -20% polymer needed for controlling acid release. Furthermore, there was reduction of drug release in buffer medium due to the increased resistance to the drug diffusion. Diethyl phthalate was included in the DR pellets formulation as hydrophilic plasticizer for its role to increase the permeability of enteric film in acid medium.

Table 5. *In vitro* drug release of prepared DR capsules

Formula code	Drug content mg/ capsule	Drug release in acid medium (%)	Drug release in buffer medium (%)
DRC1	107.4	52.9 (1.16)	93.7 (1.34)
DRC2	111.6	39.1 (1.27)	92.1 (1.38)
DRC3	118.2	40.1 (1.23)	96.4 (1.78)
DRC4	115.2	35.8 (1.42)	101.2 (1.15)

Figures in the parentheses represent ±SD, n=3.

Doxycycline hyclate release from DR capsules was studied as prescribed for doxycycline hyclate delayed release capsules in USP 24. The drug releases of all but one capsule (DRC1) were within USP 24 requirement (Table 5). The blend of DC pellets with *in vitro* release of more than 95% in buffer medium and DR pellets with release less than 15% in acid medium

and more than 70% in buffer medium (25% : 75% ratio) showed USP 24 release requirement (formulations DRC2, DRC3, and DRC4). These results reveal that sodium starch glycolate and HPMCP55 in the formulation of delayed release capsule is useful for making an effective delayed release dosage to achieve a desired release. Furthermore, the findings of the pre-formulation trial led us to conclude that successful delayed release formulation was critical on selection of appropriate amount of variables such as PVP (binder), aerosil (as an antiadherent), diethyl phthalate (plasticizer) and sodium lauryl sulphate (wetting agent). The results of role of sodium starch glycolate as a pH-dependent disintegrant in increasing the release in buffer are comparable with studies reported earlier (Gohel *et al.*, 2000 and Basak *et al.*, 2004). It may be concluded that DR capsules using HPMCP55 as an enteric polymer, sodium starch glycolate as pore forming disintegrant and other variables discussed earlier is suitable for doxycycline hyclate delayed release formulation and can help to reduce upper gastrointestinal adverse reaction to doxycycline.

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