Doxycycline Hyclate Delayed Release Capsules with Sodium Starch Glycolate as a pH-Dependent Pore Forming Agent

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Delayed release doxycycline hyclate capsules were prepared with suitable blend of doxycycline hyclate-coated nonpareil seed pellets and doxycycline hyclate delayed release pellets. The delayed release pellets were prepared by coating the doxycycline hyclate-coated pellets with hydroxypropylmethylcellulose phthalate-55 polymer solution. A concentration of polymer in the range of 15 to 20% was found to comply with drug release test as specified in the USP in acid medium but failed to meet the requirements in buffer medium (pH 5.5). The inclusion of sodium starch glycolate (1-3%) in both doxycycline-coated and delayed release pellets preparation stages was found to enhance the release of the drug in the buffer medium without altering its release in acid medium. The blend of delayed release pellets (75%) and drug-coated pellets (25%) in delayed release doxycycline hyclate capsules produced an optimum *in vitro* drug release in both the media.

Doxycycline hyclate is one of the most important semi-synthetic tetracycline derivatives with broad spectrum activity and used orally in respiratory tract infections, gonococci infections, chlamydia infections and traveller's diarrohea[1]. Side effects such as gastric irritation, oesophagitis and epigastric distress are observed due to high concentration of the drug in the stomach[2,3]. Delaying the release of 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)[4]. 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 sodium starch glycolate as a pH-dependent pore forming agent, which dissolves at pH 5.5, along with its superdisintegrant properties. The delayed release capsule was formulated by blending drug-coated pellets and delayed release pellets.

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® 200 (Coverlal and Company, Chennai) were used. All other ingredients used throughout the study were of analytical grade and were used as received.

The composition of doxycycline hyclate-coated nonpareil seed pellets (DC pellets) is shown in Table 1. The composition with respect to inclusion of sodium starch glycolate was selected to adjust drug release from DC pellets and from the blend as per predetermined limits under experimental conditions of preparations. In DCF3 and DCF4 the ratio of drug and nonpareil seeds were varied keeping the composition of the coating solution same as that of DCF2. 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

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TABLE 1: COMPOSITION OF DOXYCYCLINE HYCLATE DC PELLETS

Formula Code	Composition (%W/W) of solution						Drug (g)	Non-pareil Seed (g)
	PVPK30	SLS	SSG	Aerosil	Water	IPA		
DCF1	5.0	0.1	-	-	2.0	94.9	500	250
DCF2	5.0	0.1	0.5	0.05	2.0	94.2	500	250
DCF3	5.0	0.1	0.5	0.05	2.0	94.2	750	250
DCF4	5.0	0.1	0.5	0.05	2.0	94.2	800	250

SLS-Sodium lauryl sulphate; SSG-Sodium starch glycolate; IPA-Isopropyl alcohol

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° in a tray drier for 4-5 h.

The composition of coating solution is given in Table 2. The composition with respect to HPMCP55 concentration was selected based on trial coating. The concentration of HPMCP55 specified in Table 2 was developed as a minimum optimum concentration to adjust drug release in acidic medium as per predetermined limits. The inclusion of sodium starch glycolate was developed to adjust drug release in buffer medium. The coating solution (Table 2) was sprayed continuously at 5 g/min rate over the DC pellets bed (pre-warmed to 40°) 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°, 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: COMPOSITION OF DELAYED RELEASE COATING SOLUTION

Materials	DRF1	DRF2	DRF3	DRF4
DC pellets used	DCF1	DCF2	DCF3	DCF4
HPMCP55	10.0	10.0	10.0	10.0
Diethyl phthalate	2.0	2.0	2.0	2.0
Sodium starch glycolate	-	2.5	3.0	3.0
Aerosil	-	0.05	0.06	0.08
Solvent mixture 1	88.0	85.45	-	-
Solvent mixture 2	-	-	84.94	84.92

Solvent mixture 1 is a solution of methyl alcohol and methylene chloride (50:50); solvent mixture 2 is a solution of isopropyl alcohol and methylene chloride (30:70).

The blend of doxycycline hyclate delayed release pellets (DR pellets) and DC pellets at the ratio of 75:25 was 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 3.

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 drug content, *in vitro* drug release and pellet size by sieving. The drug content for doxycycline hyclate was car-

TABLE 3: COMPOSITION OF DELAYED RELEASE CAPSULES (BLEND OF DC AND DR PELLETS)

DR capsules	DR pellets (75%)	DC pellets (25%)
DB1	DRF1	DCF2
DB2	DRF2	DCF2
DB3	DRF3	DCF2
DB4	DRF4	DCF2
DB5	DRF4	DCF3
DB6	DRF4	DCF4

TABLE 4: *IN VITRO* DRUG RELEASE OF DC PELLETS AND DR PELLETS

Formula code	Size of pellets* (mm)	Drug content mg/ g of pellets	Drug release in acid medium (%)	Drug release in buffer medium (%)
Doxycycline hyclate DC pellets				
DCF1	0.76	338.6	102.3 (1.17)	62.6 (1.19)
DCF2	0.74	478.9	100.7 (1.18)	100.6 (1.24)
DCF3	0.78	703.1	100.3 (1.52)	96.6 (1.23)
DCF4	0.81	723.4	97.63 (1.12)	102.9 (1.78)
Doxycycline hyclate DR pellets				
DRF1	0.92	398.2	26.2 (1.12)	75.7 (1.32)
DRF2	0.91	371.4	11.2 (1.61)	73.9 (1.74)
DRF3	0.94	526.4	12.4 (1.17)	76.2 (1.22)
DRF4	0.98	497.3	10.3 (1.57)	8.7 (1.84)

*Average size of pellets was found out by sieving using the equation, $d_{av}=\Sigma$ (%retained)×(average size)/100. Figures in the parentheses represent ±SD, n=3.

ried out as per USP[5] 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[6] 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° 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 the 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%).

The results of the size of DC and DR pellets, drug content and *in vitro* release of the DC and DR pellets are given in Table 4. The *in vitro* release for DCF1 in buffer medium was found to be very less (62.5%). The inclusion of sodium starch glycolate (0.5%) and aerosil (0.05%) increased the release in buffer medium significantly. The *in vitro* release of DR pellets of the formulation DRF1 in acid was 26.20%. The inclusion of sodium starch glycolate in other formulae of DR pellets (DRF2, DRF3 and DRF4) 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 DRF3 and DRF4 did not affect the acid resistance of the film albeit it did increase the release in buffer medium.

Doxycycline hyclate release from DR capsules was studied as prescribed for doxycycline hyclate delayed release capsules in USP 24. The drug releases 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 DB2, DB3, DB4, DB5 and DB6). 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. 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[7]. It may be concluded that DR capsules using HPMCP55 as an enteric polymer and sodium starch

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 (%)
DB1	107.4	52.9 (1.16)	93.7 (1.34)
DB2	111.6	39.1 (1.27)	92.1 (1.38)
DB3	118.2	40.1 (1.23)	96.4 (1.78)
DB4	115.2	35.8 (1.42)	101.2 (1.15)
DB5	117.2	37.2 (1.12)	100.2 (1.32)
DB6	116.8	36.4 (1.74)	102.2 (1.42)

Figures in parentheses represent ±SD, n=3.

glycolate as pore forming disintegrant is suitable for doxycycline hyclate delayed release formulation and can help to reduce upper gastrointestinal adverse reaction to doxycycline.

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REFERENCES

1. AHFS Drug Handbook, 2nd Edn., American Society of Health-System Pharmacists, Lippincott Williams and Wilkins, Philadelphia, 2003, 443.
2. Liebowitz, B.J., Hakes, J.L., Cahm, M.M. and Levy, E.J., **Curr. Ther. Res.**, 1972, 14, 820.
3. Collens, F.J., Mathews, H.R., Baker, S.E. and Strakova, J.M., **Brit. Med. J.**, 1979, 278, 1673.
4. Reynolds, J.E.F., Eds; In; Martindale, The Extra Pharmacopoeia, 30th Edn., The Pharmaceutical Press, London, 1993, 160.
5. The United States Pharmacopoeia 24, The United States Pharmacopoeial Convention, Rockville, MD, 2002, 610.
6. The United States Pharmacopoeia 24, The United States Pharmacopoeial Convention, Rockville, MD, 2002, 1942.
7. Gohel, M.C., Amin, A.F. and Iyer, L., **Int. J. Pharm. Excipients**, 2000, 15, 192.