Development and stability evaluation of enteric coated Diclofenac sodium tablets using Sureteric

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Abstract: This study was aimed to develop a stable enteric coated diclofenac sodium tablets using Sureteic without a subcoating layer. Diclofenac uncoated tablets were developed and manufactured through the non direct compression process. Sureteric white aqueous coating dispersion was used as enteric coating material. Sureteric is a special mixure of Polyvinyl Acetate Phthalate (Phthalavin®, PVAP), plasticizers and other ingredients in a suitable optimized dry powder formulation. The obtained enteric coated tablets were subjected to disintegration and no sign of cracking was observed when they placed in a hydrochloric solution at pH 1.2, but they were completely disintegrated within 10 minutes when they putted in buffered solution at pH6.8. Dissolution test was also conducted by placing tablets in 0.1 M HCl for 2 hours and then 1 hour in phosphate buffer at pH 6.8. Less than 0.9% of drug was released in the acidic phase and up to 97% in the basic medium. These results show that Sureteric can be successfully used to produce diclofenac sodium enteric coated tablets in order to prevent its release in the stomach and facilitate immediate release of the drug in the duodenum. These findings suggest that aqueous enteric coating with Sureteric system is an easy and economical approach for preparing stable diclofenac sodium enteric coat without the use of a subcoating layer.

Keywords: Diclofenac sodium, tablets, enteric coating, aqueous dispersion system, Sureteric.

INTRODUCTION

Film coating is the more contemporary and thus commonly used process for coating oral dosage forms (Aulton, 2007). It consists of the deposition of a thin layer of a polymer formulation to the surface of an oral solid dosage form. This will confer specific benefits that broadly range from: (i) improving the visual qualities of the dosage form, (ii) masking unpleasant organoleptic properties, (iii) easing ingestion, (iv) improving product stability and (v) modifying the release profile of the drug. Enteric film coating are intended to either protect the drug from the pH of the stomach (in the case of acid – vulnerable drugs) or protect the stomach from the irritant effect of certain drugs such as NSAIDs. This phenomenon can be achieved by using polymers formulations where these polymers are soluble at pH value in excess of 5-6. Indeed, polymer for enteric coating can be applied to a wide range of solid dosage forms including tablets, capsules, granules, or pellets, Several polymers are used as pH-sensitive enteric coating materials. Among these polymers cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, methacrylic acid copolymers (Guo *et al*., 2002) and acrylic copolymers (Porter 2006) were frequently recommended. Recently PVAP (polyvinyl acetate phthalate) was considered as one of the most preferred materials for designing enteric coating formulations in terms of performance and global acceptability (Colorcon). In fact, PVAP is commonly used in the pharmaceutical formulation polymer, especially as enteric coat for tablets and/or capsules.

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The aqueous based coating systems are preferred when compared with the organic solvent based systems. In fact, organic solvents based coating systems have many drawbacks including environmental pollution, explosion, and risk of toxicity for operators (Baudoux *et al*., 1990; Durriya *et al*., 2008; Bushra *et al*., 2010).

Sureteric is an optimized, one-step, pigmented, aqueous polymer, providing an enteric, gastric resistant film coating for oral solid dosage forms. In fact, the obtained film coats resists to gastric juice but immediately starts to dissolve at a pH higher than 5.5. Sureteric is a special mixture of Polyvinyl Acetate Phthalate (Phthalavin® enteric coating polymer, PVAP), plasticizers and other components. The obtained dry powder formulation is developed as an alternative to acrylic polymer systems for aqueous enteric coating of tablets and/or capsules. It offers consistent, reproducible enteric release characteristics which ensure the desired product performance. The obtained enteric coating support gastric guise as well as the severity of handling, packaging, transportation, and storage. Moreover, sureteric is a cost effective option that uses simple coating pan and is both easy to prepare, and clean up (www.colorcon.com). A subcoating layer is usually recommended to strengthen friable cores or to avoid incompatibilities between the pharmaceutical active ingredients and the enteric coat formulation. Indeed, the stability of alkaline drugs coated with acidic polymers, such as the case of acrylic or phthalic polymers used in enteric coat, can be compromised due to acid base interaction between the acidic polymer and the alkaline drug (Danget *et al* 2000). When compared with Almost all non-steroidal anti-

inflammatory drugs, diclofenac sodium causes gastric irritation which may results in ulceration by inhibiting the prostaglandins synthesis which has protective action on gastric mucosa. This cause of formation of ulcer at different levels of the gastrointestinal tract (Derle *et al*., 2006). Diclofenac sodium is an alkaline substance which may interact with acidic polymers used in enteric coating and thus may require a subcoating step to minimize this effect. But this step is a time and material consuming and it may increase the final cost of the enteric coated tablets. Therefore, this study aims to develop enteric coated diclofenac sodium tablet using Sureteric as coating material and to evaluate the stability and quality of the obtained tablets in absence of a subcoating layer.

MATERIAL AND METHODS

Materials

Diclofenac sodium (Aarti Drug Limited, India), cellulose microcrystalline (Avicel pH 101; FMC Corp, Ireland), Plasdone (ISP Switzerland), Aerosil (Evonik, Germany), sodium starch glycolate (DMV-Fonterra, Holland) and magnesium stearate (Magnesia, Germany), Lactose monohydrate (Friesland foods, Netherland), Starch from (Galam, Israel). Sodium hydroxide (Merck, KgaA, and Darmstadt, Germany) monobasic potassium phosphatem (Merck, KgaA, Darmstadt, Germany) and all the other chemicals used were of analytical grade and obtained from commercial sources. The enteric coating material was methacrylic acid copolymer based pigmented Sureteric white material was provided by Colorcon GmbH (Germany), Propylene Glycol (The Dow Chemical Co.). Ethanol Internal (Gadot Chemical Co., Israel). Aluminum foil (INEOS) and PVC (Klockner Pentaplast).

Instruments

The HPLC system, Merck Hitachi, (Interface module D-7000, Autosampler L-7200, Pump L-7100, Detector L-7450) was used for the analysis and quantification of diclofenac sodium in the samples study. Separation was accomplished with a 250 mm X 4.6 mm 57 L7 (Octylsilane chemically bonded to totally porous silica particles, 5.0 µm in diameter). An electronic balance (Precisa 205 ASCS), was measured using vernier caliper for thickness and diameter, TA-100 Erweka friabilator) , hardness tester (Pharma test PTB311E), A model ZT-221disintegrator tester (Erweka, Husenstamn, Germany) was used for disintegration testing. A dissolution apparatus (Erweka DT 70, Husenstamn, Germany) was used for drug release testing. The tablet coating was performed in coating pan (Erweka GmbH., type UG, Frankfurt, Germany) using external spray gun, dryer and (Type :Ceccato air compressor S.p.A, mod:8566 Mfg by CDA Engineering sdn Bhd-Malysia. Packing machine (Ulhmann-200, Germany). Humidity chamber for accelerated stability study (Binder GmbH Bergster, Tullingen, Germany).

Method

Preparation of uncoated Diclofenac sodium (50 mg) Tablet

Diclofenac sodium uncoated granules were prepared by Pharmacare PLC. All the ingredients were accuratelly weighed and sieved through 24 mesh sieve. The uncoated tablets were composed of avicel pH 101, lactose monohydrate, sodium starch glycolate, starch, plasdon k-29/32, aerosil and magnisum stearate. The involved preparation process was a wet granulation method, the dried granules were lubricated by magnesium stearate, and the obtained flowable granules were compressed using Manesty tableting machine. The average weight of the final uncoated tablets was about 270 mg and it was within the limit of ± 5%. After compression, physical appearance, hardness, weight variation and drug content of diclofenac sodium uncoated tablets were evaluated according to the USP tests (USP 2007). Dissolution assay was also determined according to the procedure reported by the USP were the paddle was operated at 50 rpm using 900 ml pH 6.8 phosphate buffer maintained at 37°C. Only after passing all the above USP tests diclofenac sodium uncoated tablets were selected for coating.

Enteric coating of diclofenac sodium (50 mg/tablet)
Preparation of Sureteric for Enteric Coating

1000 ml of distilled water was weighed into a mixing vessel and stirred to form a vortex. 300 g Sureteric white powder was accurately weighed and added to the center of the liquid vortex in a slow steady stream, avoiding clumping and maintaining a vortex. Mixing was continued for around 20-25 minutes. Before starting the coating process, sureteric aqueous dispersion was passed through a 250 µm sieve. The aqueous enteric coating dispersion was maintained under continuous stirring during the coating process. Both coating dispersions were prepared according to the technical document and guidelines provided by Colorcon.

Coating methodology (Pl. check lower/upper case)

Tablet coating was performed in a conventional coating pan (Erweka G.m.b.H., Module: AR402, Serial No. 11356.03e, Frankfurt, Germany) with one spray gun. The coating pan was previously cleaned using alcohol 95%. A batch size of 3.5 kg diclofenac sodium core tablets was selected for coating. The core tablets were loaded into the coating pan. Tablet cores were pre-heated to about 40°C utilizing a dryer and air compressor (Type: Ceccato air compressor S.p.A, mod: 8566 Mfg by CDA Engineering sdn Bhd-Malysia). Warm air was introduced into the coating pan (up to 50–55°C) during the entire coating process. The spray gun was filled with Sureteric white aqueous dispersion and operated at a proper flow rate. The pan was set into motion and seal coating dispersion was sprayed on to the falling cores under a suitable air pressure (87.0-116.0 psi) 6-8 bar. The air heater was switched off and tablets were blow dried for 20-25

minutes in the coating pan. The core tablets gained 10±2% weight after coating with Sureteric. Tables 1 and 2 list the coating conditions and parameters.

Table 1: Parameters of coating process

Factor	Conditions
Equipment	Erweka Coating Pan
Substrate	50 mg Diclofenac sodium tablets
Pan Charge	3.5 Kg
Dispersion solid content	15.0%(w/w)
Pan speed	14 rpm
Inlet Temperature	52-58^{o}C
Exhaust air temperature,	40-42^{o}C
Bed Temperature	35-40^{o}C
Spray rate	50 g/min
Distance Between spray gun and tablet bed	15 cm
Coating time	min 160

Additional considerations

1. Always maintain a negative air pressure in the pan (more air out than in).
2. After start-up, allow a minimum of 15 minutes for exhaust temperature to equilibrate before making changes in fluid and/or air flows.
3. To achieve highest enteric quality and adhesion between the core and enteric interface, the spray rate of sureteric should be reduced by 15%, for the first 1% weight gain, if any tackiness or sticking is noticed.
4. Once Sureteric delivery has begun, keep a constant flow rate.
5. Keep gun needles in an open position during the coating process (Colorcon).

Table 2: Parameters of coating formulation

Parameter	Coating
Theoretical weight gain (mg)	10 ±2%
Propylene Glycol	2.5% (w/w)
Deionized water	72.5% (w/w)

Evaluation of diclofenac sodium (50 mg) coated tablets

Weight uniformity of coated tablets

Randomly selected twenty tablets were weighed individually and together. Average weight was calculated. Each individual tablet weight was compared against the calculated average.

Mechanical strength

The hardness of the coated tablets was tested using a tablet hardness tester. This test was conducted according to the USP specification. 20 randomly selected tablets from each of three study batches were tested at the different time intervals of the study.

Disintegration test of enteric coated tablets

The disintegration time of enteric coated diclofenac sodium 50 mg tablets was determined according to the procedure reported in USP (USP 2007). Six tablets of diclofenac sodium enteric coated tablets were weighed individually and placed in acid phase (0.1 N HCl) for 2 h in a USP basket rack assembly (Erweka ZT-2, Husenstamn, Germany) after which they were removed and inspected for cracking or disintegration. The same tablets were then placed in phosphate buffer, pH 6.8 and observed for disintegration.

Assay for enteric coated tablets

The amount of diclofenac sodium in each tablet was determined according to the USP assay method (USP 2007).

Dissolution test of enteric coated tablets

The dissolution test for enteric coated tablets was performed according to USP (USP 2007) adopting method B in pH 1.2 and pH 6.8 buffers. Drug release was measured in a USP dissolution bath using apparatus II at 50 rpm. In the first stage (pH 1.2); the tablets were putted in 900 mL of 0.1 N hydrochloric acid in a USP dissolution bath (Erweka DT 700, Husenstamn, Germany), equilibrated to a temperature of 37±0.5°C. The paddle stirring rate was set at 50 rpm. Six tablets were introduced into the apparatus and the apparatus was run for 2 h. After the operation outlined above, an aliquot of the fluid was drawn, and the second stage (pH 6.8) was commenced. This last consisted of a phosphate buffer of pH 6.8 prepared by mixing 0.1 M hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1). The apparatus was operated for a further 45 minutes. At the end of the time period, an aliquot of the fluid was drawn. Samples were assayed by HPLC method, at 254 nm wave length.

Stability study of coated tablets

Samples of Diclofenac sodium enteric coated tablets were blister packed in aluminum foil and PVC. These samples were then subjected for stability study according to ICH guidelines where zone II was selected as storage conditions (ICH 2003). Tests were conducted at room temperature (RT) and accelerated stability conditions. The samples were designated as time 0, 3, 6, 9, 12, 18 and 24 months for RT and 0, 1, 2, 3 and 6 month for accelerated studies. Samples designed for RT storage were kept at 25±2°C and 60±5% relative humidity (RH). The samples in the accelerated stability study were kept at 40±2°C and 75±5% RH in humidity chamber. Samples were tested for its appearance, disintegration, dissolution and assay using the previously described procedure to evaluate the stability of coated tablets. The percent dissolution, assay, appearance and hardness of the coated tablets stored at room temperature for 24 months are shown in table 6.

RESULTS

The use of Sureteric white as enteric coating material gave successful results of enteric coating. In order to achieve good coating results, uncoated tablets should have good physical parameters to withstand the coating steps. Therefore, Diclofenac sodium tablet cores were successfully prepared by a non direct compression method using Avicel pH 101 as filler/ binder, Starch as disintegrant, Lactose monohydrate as filler, plasdone as binding agent, sodium starch glycolate as disintegrating agent, aerosol as glidant and magnesium stearate as lubricant. The obtained dry and appropriately lubricated granules had good flowability resulting in low tablet weight variation. The granules were compressed without any problem and the prepared tablets were free from defects such as capping and lamination. Tablets of good mechanical strength (good breaking force higher than 7.0 Kg/Cm^2) and low friability (a maximum loss of mass not greater than 1%) were manufactured. Physical appearance, hardness, friability, weight variation and drug content evaluation of the uncoated tablets were found to be satisfactory under pharmacopoeial standards of tablet evaluation as shown in table 3.

Table 3: Characteristics of core tablets.

Average weight in mg (within the limit ± 5%)	Average hardness (kg/cm^2)	Friability	Average disintegration time
270	7.5+1.2	0.13%	Not more than 10 minutes in water

In fact, tablets used in enteric film coating process must be sufficiently hard to bear mechanical stresses and should show a very low potential for erosion and edge chipping. In fact, any defects in the tablet core may result in localized weakness of enteric film coat. Tablets were coated smoothly without having any physical visible defects such as orange peel effect, chipping, tacking or other flaws. Although traditional aqueous enteric coating systems can require multiple component mixing steps before coating, this novel system was dispersed in only one step in the minimum amount of time, and produced acceptable weight gains. In fact, this system is dry, dispersible powder that does not require the use of any additional plasticizer, detackifiers or neutralization agents. The average final weight of 20 coated tablets was 297 and this means a weight gain of 10+2%. The weight variation was found to be with-in the official limit 5%. The obtained coated tablets were robust since, the hardness of 20 coated tablets was measured and the average was 8.6+0.4 Kg/Cm^2 for batch I, 9.7+0.2 Kg/Cm^2 for batch II and 9.1+0.5 Kg/Cm^2 for batch III (table 4).

Table 4: Evaluation of three different batches of diclofenac sodium coated tablets.

Quality Parameter	Batch I	Batch II	Batch III
Physical appearance	Complies	Complies	Complies
Average weight in mg (Within the limit ± 5%)	297.28	296.7	296.6
Hardness (Kg/cm2)	8.6 ± 0.4	9.7 ± 0.2	9.1 ± 0.5
Drug content	100.8 ± 0.77	100.42 + 0.9	99.96 + 1.9
% dissolution diclofenac sodium in pH 1.2	0.3714 ± 0.65	0.457 ± 0.78	0.457 ± 0.83
% dissolution diclofenac sodium in a buffer pH	98.24 + 2.7	96.94 ± 1.9	96.82 ± 4

The efficiency of the coating was determined by subjecting the coated tablets to gastric pH, and drug release was analyzed using HPLC system. Results of disintegration and dissolution are shown in table 5 and 6.

Table 5: Disintegration of diclofenac sodium (50 mg/tablet)

Media	Results
0.1 N HCl solution, pH 1.2	No signs of cracking or softening was observed
Phosphate buffer pH 6.8	Tablets were completely disintegrated within 10 minutes

DISCUSSION

The aim of this study was to develop enteric coated diclofenac sodium 50 mg/ tablet by using Sureteric without a sub-coating step. Enteric coating was successfully done using Sureteric white coating aqueous dispersion. The preparation of this aqueous dispersion is easy and requires short time which decreases the cost of the coating process. Sieving was done to separate non dispersed particles of polymer that may result in gun needle obstruction or alteration of the smoothness of the enteric coat. The dispersion was stirred during the experiment to avoid sedimentation and coalescence of particles. Tablet coating was carried out in conventional coating pan using spray coating technique. During coating, certain parameters require great care such as temperature of coating pan and the spray rate of coating dispersion. If these are not maintained properly, they affect the smoothness and uniformity of coating. In fact, some process parameters of potential importance, including the temperature of **c**oating pan and the spray rate of the coating solution were investigated by other researchers (Sauer *et al*, 2007; Parikh *et al*., 1993;

Table 6: Percentage of assay and average of drug release from enteric coated Diclofenac sodium (50 mg)/tablet in 0.1 NHCl and pH 6.8 phosphate buffer (stored at room temperature for 24 months)

Period (months)	Physical appearance	Hardness	% dissolution diclofenac sodium in pH 1.2	% dissolution diclofenac sodium in a buffer pH 6.8	% assay
0	complies	9.5±1.43	0	96.0±2.2	100.5±1.6
3	complies	8.7±0.3	0	94.5±1.8	99.3±0.8
6	complies	11.12±0.6	0	93.6± 1.8	100.1±1.2
9	complies	11.7±0.89	0	97.1±2.3	101.1±0.9
12	complies	10.7±1.3	0	99.9±2.03	101.9±1.4
18	complies	10.8±0.7	1.2	99.79±1.1	99.83±01.2
24	complies	11±0.8	1.8	100.46±1.5	100.03±1.16

Krogars *et al*, 2000). At low spray rates, the temperature of the coating pan did not affect the roughness of the coated tablets. At higher spray rates, higher temperature gave smoother films. In another study, process variables investigated were inlet airflow, pan speed, inlet air temperature, coating time, atomization pressure, and fan pressure. Pan speed and coating duration were also identified as variables significantly affecting content uniformity (Rege *et al*, 2003). It was shown that lower rates of drug release from the coated tablets may be obtained by using high inlet-air temperature and low spray rate of the polymeric dispersion during coating. In fact, Frisbee *et al* reported that the properties of final products are affected when temperature is increased for various time periods to remove water and solvent from the product (Frisbee *et al*., 2003). Sometimes, a sub-coating step may be required to increase the strength of friable cores before the application of the enteric coat. This sub-coat may also be necessary to prevent interaction between the pharmaceutical active ingredient and the coating formulation. But pharmaceutical manufacturers tend to waive on this step due to the higher process time, complexity, cost and environmental pollution due to the use organic solvents. In the present study sub-coating was avoided and the obtained coated tablets were stable, indicating high compatibility between diclofenac sodium and the used Sureteric. Accordingly, this result in a decrease of the cost of the coating process if compared with other ready to use enteric coating materials that require the sub-coating step (Anroop *et al.*,2010, Putta et. al 2011 and http://www.isppharmaceuticals.com).The coated tablets had no visible defects or signs of peeling or chipping. Tablets showed complete acid resistance for 2 h (Figure 1). In fact, diclofenac sodium release met the criteria outlined in this study i.e. not less than 80% dissolved after 60 minutes in buffer pH 6.8. Tablets were stored in a temperature and humidity controlled chamber to observe the stability of the formulation. Results of stability testing were satisfactory, showing no significant variation in physical characteristics, color, hardness or disintegration time of coated tablets. In vitro drug release studies were carried out since these are considered the best tool for assessing in vivo drug behavior. Percent dissolution and assay were within the acceptable limits of USP (table 5 and 6). Three batches of coated diclofenac sodium were prepared and the previously mentioned parameters were tested under the same conditions. The results obtained from the three batches showed no significant differences for each set of these batches (table 4 and figure1.). This indicates that this manufacturing process is reliable and reproducible.

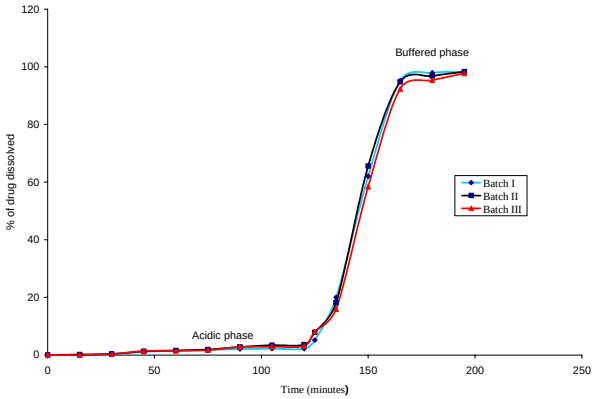

Fig 1: Drug release from three different batches of Diclofenac sodium tablets in 0.1 N HCl and pH 6.8 phosphate buffer.

CONCLUSION

A delayed release diclofenac sodium (50 mg) formulation was developed using Sureteric system without using a subcoating layer. Aqueous enteric coating was successfully conducted under lab-scale facilities. Sureteric system provides acceptable enteric performance in 0.1 N HCl and pH 6.8 phosphate buffer. The produced coated tablets were stable within 24 months when stored at room temperature. Three batches were produced and tested under the same conditions. All batches showed the same results which means that this formulation is reliable and reproducible process. Therefore, these findings suggest that aqueous enteric coating with Sureteric system is an

easy and economical approach for preparing stable diclofenac sodium delayed release tablets.

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