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Research Article

Development of an Aqueous Film Coating of Metformin Hydrochloride Tablet: Influence of Plasticizers and Surfactants on Coating Properties

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Abstract

Hydroxy Propyl Methyl Cellulose (HPMC) 5cPs, an aqueous soluble polymer was employed for enteric coating metformin hydrochloride (Met-HCl) tablets 250mg. Proper optimization for the aqueous based film coating formulation was undertaken primarily employing plasticizers like polyethylene glycol (PEG) 400 and propylene glycol (PG). The defect free selected formulations were further subjected for studying the effects of surfactants like Sodium Lauryl Sulphate (SLS) and Tween-80 along with the plasticizers. The quality of the aqueous film coats or the plasticizer efficiency in case of PEG-400 is in the order 1.5%>0.5%>1.0% and for PG 1%> 4%> 3% which can be stated on the basis of less incidence of major coat defects like chipping, cracking, orange peel, roughness, blistering, blooming, picking. The quality of aqueous film coat or the surfactant efficiency in case of SLS+PEG-400 is in the order 0.3%< 0.5%< 0.1% and SLS+PG is in the order 0.5%< 0.1%< 0.3%. In case of Tween-80+PEG-400 the order is 0.3%< 0.5%< 0.1% and Tween-80+PG is in the order 0.3%< 0.1%< 0.5%. Elegant film formation can be stated from fewer incidences of coat defects. The obtained coated tablets eventually satisfied all the normal physical parameters like thickness, weights, and weight gain, drug content, crushing strength, percent friability, disintegration time, dissolution profile and possible drug-polymer interactions. ANOVA was undertaken followed by Dunnet multiple comparison for the dissolution profile considering uncoated as the standard. The difference was considered significant at $p \leq 0.01$.

Keywords: Aqueous film coating, metformin hydrochoride tablets, plasticizer, surfactants.

Introduction

Film coating is a complex process that involves different factors. To ensure spreading and/or film forming capability plasticizers are added. The type and concentration of plasticizers can affect the film properties, as revealed by several investigations [1-3]. The plasticizing efficiency is measured by the lowering of the incidence of coat defects. In this study two plasticizers namely polyethylene glycol 400 (PEG-400) and propylene glycol (PG) were selected. Aqueous film coating liquid was prepared by incorporating different concentrations of PEG-400 and PG [4-5].

As the viscosity of the coating solution increases, there is greater resistance to spreading on the substrate surface and reduced tendency of the droplets to coalesce, both of which increase surface roughness. Other factors arising from an increase in solution viscosity, which may potentiate surface roughness, include the larger mean droplet size on atomization and the reduced penetration into the uncoated tablet or multiparticulate surface [6-8]. Variation in solution viscosity may also affect the rate and extent that a coating formulation penetrates into a substrate during the application. Difference in penetration behavior may be important in determining the adhesion of the coat to the substrate [3,9,10]. Little or no penetration may lead to poor adhesion. Invariably a tablet formulation includes lubricants to improve flow properties of the granules and to overcome certain processing problems. These ingredients are hydrophobic and in fine state of subdivision, present on the surface of the tablet which may hinder penetration of the coating liquid / solution. It is therefore prudent to include surfactants of high HLB value at smaller concentration, to improve penetration and spreading properties of the coating liquid.

The objective was also to investigate the effects of surfactants on the coating uniformity and quality of the film coat. In this study two surfactants of high HLB value such as sodium lauryl sulphate (SLS) and Tween-80 were selected and incorporated at different concentrations in the coating solutions [11-12].

Diabetes is one of the major causes of death and disability in the world. World Health Organization (WHO) estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. Metformin hydrochloride (Met-HCl) is a biguanide derivative of highly water soluble oral anti hyperglycaemic agent used in the treatment of type II non-insulin dependent diabetic mellitus (NIDDM). Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea, and diarrhea, may occur during the treatment [13]. Gastrointestinal absorption of Met-HCl is incomplete with an absolute bioavailability of 40–60% (under fasting conditions) and in combination with rapid elimination and 20–30% of an oral dose is recovered in faeces. It decreases as the dose increases, suggesting some form of saturable absorption or permeability/transit time-limited absorption[8]. Administration of enteric coated Met-HCl form could reduce the dosing frequency and improve patient compliance. In order to achieve an optimal therapy, the effort mainly focuses on formulation of an enteric coated tablet of Met-HCl dosage forms [14].

Our present study is aimed in the preparation of a 250mg Met-HCl tablet and subsequent development of an optimized film coating formula after properly studying the effects of plasticizer and surfactants for the purpose of coating the tablets [14-15].

Materials and Methods

Materials

Metformin hydrochloride was obtained as gift sample from Intas Pharmaceuticals, Bagheykhola, Sikkim, India. HPMC 5 cps was

purchased from the Dow Chemical Company, USA. PEG-400, Propylene glycol (PG), Dicalcium phosphate, SLS and Tween-80 were purchased from LOBA Chemie, Mumbai. Corn starch was purchased from Hi Media. Talc, magnesium stearate and sodium hydroxide was purchased from Merck. Titanium Dioxide was purchased from Qualigens. Fruit colours were purchased from Bush Chem. All the chemicals and solvents were of analytical grade.

Preparation of the tablets

Met-HCl tablets 250mg were prepared by the process of wet granulation in a lab scale wet granulator (Shakti Engneering, India) (Table 1). Required quantities of corn starch were mixed with water gradually on a hot air oven until a semi-solid paste was formed. This paste was treated as a binder and gradually added to the granulator already containing the required quantities of drug and other excipients. The gralulator was operated until a proper mix was obtained. The semisolid mix was passed thorough sieve no. 10 and subjected to tray drying on an electronic tray drier (SAMS India Ltd, India). The dried granules was collected and further passed through sieve no.16. Required quantities of talc, magnesium stearate and aerosol were added and subsequent compressed with 10mm biconcave punches on a 16-station rotary punching device to produce tablets (Cadmach, India) (Table 1).

Table 1. Composition of Met-HCl tablets

Composition	Purpose	Quantity for 1 Tablet (mg)
Metformin Hydrochloride	API (Active pharmaceutical ingredient)	250
Maize Starch (paste)	Binder	55
Dicalcium phosphate	Exepients	141
Potato Starch (dried)	Disintegrant	40
Aerosil	Flow promoter	3.5
Magnesium stearate	Lubricant	7
Talc	Glidant	3.5
Total weight		500

Preliminary coating procedure

Two hundred tablets of Met-HCl were loaded on a lab-scale pan coater (SAMS ltd, India) previously cleaned, dedusted. The coating liquid was filled into the spray gun with pneumatic pump attachment (Hi Power Pneumatics, India). The pan was rotated at 40 rpm for obtaining a cascading fall of the tablets. All the parameters were previously adjusted with dummy tablets (Table 2). As the tablets rolled, the film forming liquid was sprayed intermittently allowing the solvent to evaporate. The process was continued until all the coating solution was used up [4-6].

Table 2: The different adjusted process variables

Process variables	Adjusted specifications
Pan design/Baffling	12 feet diameter with no baffles
Rotational speed of pan	40 rpm
Spray pressure (operational)	60±5 Pound per square inch (p.s.i) (value represent mean SD (n=3)
Bed to Gun distance	1±0.5 feet (value represent mean SD (n=3)
Bed temperature	32- 35°C
Dry air temperature	60±5°C
Spray pattern type	Circular, occasionally elliptical
Pan load	70 gm

Procedure for the preparation of film coating liquid involving plasticizers

In a 500ml clean beaker about 125 ml of purified water was measured and the weighed amount of polymer HPMC 5cps was added and allowed to soak overnight. Next morning it was stirred using a magnetic stirrer (Remi motors, India) for 5-7 min to get a uniform dispersion of the polymer solution. Other ingredients such as plasticizer, opacifier, colouring agent were added gradually in required quantities (Table 3).

Table 3. Formula for film coating formulations involving plasticizers

Ingredients	F1 (%) w/w	F2 (%) w/w	F3 (%) w/w	F4 (%) w/w	F5 (%) w/w	F6 (%) w/w
HPMC 5cPs	7.5	7.5	7.5	7.5	7.5	7.5
Poly ethylene glycol-400 (PEG-400)	0.5	1.0	1.5	-	-	-
Propylene Glycol (PG)	-	-	-	1	2	3
Fruit colours (Sunset yellow)	0.6	0.6	0.6	0.6	0.6	0.6
Titaniumdioxide	3	3	3	3	3	3
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

The simultaneous evaluations are reported (Table 4). The selected formulations F3 and F4 were further tried for the effect of two surfactants namely SLS and Tween-80 and all the ingredients were added gradually in required quantities (Table 5). The simultaneous evaluations are reported (Table 6).

Table 4. Visual observation for defects in the formulations containing plasticizers

Defects	F1	F2	F3	F4	F5	F6
Blistering	++	−	−	−	−	−
Blooming	+++	−	−	−	++	+
Chipping	+++	+++	+	++	+++	++
Cracking	++	−	−	−	−	−
Orange peel	−	+++	−	−	−	−
Picking	−	+++	−	−	++	−
Roughness	++	+++	++	−	++	++
Splitting	+++	++	+	+	+++	+
Thickness of cast film (mm)	0.2	0.3	0.2	0.1	0.2	0.2
Weight gain (%)	25	23.64	21.62	10.13	18.24	21.62

(value represent mean SD (n=3), Yes- (+++), No- (--), Slight- (++), Very slight- (+)

Table 5. Formula for film coating involving plasticizers and surfactants

Ingredients	F3A	F3B	F3C	F4A	F4B	F4C	F3D	F3E	F3F	F4D	F4E	F4F
HPMC	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
PEG-400	1.5	1.5	1.5	-	-	-	1.5	1.5	1.5	-	-	-
PG	-	-	-	1.0	1.0	1.0	-	-	-	1.0	1.0	1.0
Titanium dioxide	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Surfactants (SLS)	0.1	0.3	0.5	0.1	0.3	0.5	-	-	-	-	-	-
Tween-80	-	-	-	-	-	-	0.1	0.3	0.5	0.1	0.3	0.5
Fruit Color	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

weights were taken on % w/w basis

Table 6. Visual observation for defects in the formulations containing plasticizers and surfactants

Defects	F3A	F3B	F3C	F4A	F4B	F4C	F3D	F3E	F3F	F4D	F4E	F4F
Blistering	+++	−	−	+++	−	−	−	−	−	−	−	−
Blooming	−	−	++	++	−	−	+++	+	−	++	++	++
Chipping	+++	−	−	+++	−	++	−	+++	++	++	−	++
Cracking	−	−	−	−	−	−	−	−	−	−	−	+++
Orange peel	−	−	−	++	+++	−	+++	−	−	−	−	++
Picking	−	−	−	−	+++	−	−	−	−	−	−	−
Roughness	++	−	++	++	+++	−	+++	++	−	−	−	+++
Splitting	++	−	+++	−	−	++	−	+++	++	++	−	+++
Thickness of cast film (mm)	0.33	0.23	0.30	0.30	0.40	0.30	0.33	0.23	0.10	0.10	0.10	0.30
Weight gain (%)	23.64	21.62	25.15	22.63	18.24	23.64	18.24	22.63	23.64	20.13	22.63	25.10

Yes- (+++), No- (--), Slight- (++), Very slight- (+)

Preparation of simulated intestinal fluid (SIF)

One litre of phosphate buffer pH 6.8 (PB-6.8) was used as the primary solvent. Male Wister rats are sacrificed and the rat caecum was collected. The fresh caecum was transversely sectioned and the caecum contents were added to the PB-6.8. The contents were mixed properly with a stirrer (Remi motors, India). Finally the beaker containing PB-6.8 along with the rat caecal contents was incubated (Spac n service, Kolkata, India) at a temperature of 27±2°C for 2 days. The final solution was filtered; pH was checked and was used for the purpose of dissolution as SIF.

Determination of different parameters for the evaluation of prepared coated tablets

The selected coated tablets were evaluated for their thickness, weights, weight gain, drug content, diametral crushing strength, percent friability, disintegration time, dissolution profile, drug-polymer interactions.

Tablet weight gain

Six coated tablets were randomly selected from each batch and the weight was determined individually in an electronic balance (Sartorius, India). The average weight of six tablets was calculated. The difference in the average weight with respect to the average weight of the uncoated tablet gave the weight gain of the coated tablet and the percentage weight gain was calculated accordingly and reported (Table 7).

Film thickness measurements

Six coated tablets were randomly selected from each batch and the thickness was measured individually using a slide calipers. The difference in the thickness with respect to the uncoated tablet gave the coat thickness. The cast film thickness measurement was done by using a film thickness tester (Baker dial gauge- type J17, India) by peeling off the adhering films from the substrate surface. Uniformity in thickness was measured by selecting four different zones of the cast films [4]. The average of each formulation is noted (Table 7).

Disintegration test

Disintegration tester (Campbell electronics, India) was used to determine the resistance or disintegration time of the selected five aqueous film coated tablets. Six tablets were randomly selected from each batch and one tablet was placed in each of the six tubes. The basket rack was positioned in a one-liter beaker containing purified water at 37±0.5°C. Perforated auxiliary discs were placed on the top.

The instrument was operated and the time taken for a tablet to disintegrate and all the particles to pass through the No.10 USP mesh aperture was noted according to USP/NF/IP until a palpable mass remains [4]. The average time is reported (Table 7).

Table 7. Evaluation parameters for uncoated and selected coated tablets of Met-HCl

Parameters	Uncoated	F3B	F4E	F4	F3	F4C
Thickness (mm)	5.5	5.7	5.7	5.6	5.7	5.8
Cast film thickness	–	0.2	0.21	0.15	0.2	0.33
Weights (mg)	300.0	340.0	342.5	340.5	345.0	350.0
Diametral hardness (kg/cm2)	4.8	5.2	5.3	5.1	5.4	5.4
Friability (%)	0.34	0.03	0.10	0.08	0.06	0.04
Disintegration time	2.33min	2.50min	3.03min	2.66min	2.90min	3.16min
Weight gain (%)	0	13.33	14.16	13.5	15.0	16.66
Assay (%)	98.24	98.74	98.16	95.85	97.66	94.92

Values represent mean SD (n=3)

In vitro release studies

In vitro drug release from tablets was studied using a USP –II type dissolution apparatus (paddle type) in TDT 08L model (Electrolab, Kolkata). The study was carried out in 900 ml of SIF at 37±0.5 ºC. Sink condition was maintained for the whole experiment. Ten milliliters of the sample was withdrawn at regular intervals and the same volume of warmed (37±0.5ºC) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered and the drug content in each sample was analyzed at 233nm by Shimadzu UV-1700 pharma spectroscopy, Japan.

Statistical analysis

The significance of difference between the dissolution of different studied formulations considering uncoated formulation as the standard was evaluated using the analysis of variance (ANOVA) followed by Dunnett Multiple comparison test. The difference was considered significant at p≤0.01. These statistical calculations were performed using Graph pad Instat computer program (Sep-11, 2003; Graph Pad Software, San Diego, CA) [5].

Fourier transform Infrared Spectra (FT-IR)

Infrared spectra of the pure drug, uncoated Met-HCl tablets and HPMC 5cPs coated Met-HCl tablets dispersed in KBr were recorded on a FT-IR spectrophotometer (Model-FTIR 8400S, SHIMADZU, Japan). The disc method was employed to study the possible interactions between the drug and the selected polymer HPMC (5cPs). KBr (IR Grade) discs in a proportion of 1:100::sample:KBr, were prepared from the samples and eventually analyzed over a range of 4000-400 cm-1. Transmittance (T) of the spectra were recorded and displayed [7,9].

Scanning electron microscopy

Tablet samples (F3B) were removed from dissolution apparatus at predetermined time intervals (0min, 30min, 1h) and films were scrapped off by sectioning transversally from the concave face of the tablet. The specimen was then placed on a sample holder so as to present surface and cross sectional view of the tablet to the microscope. Samples were coated with gold and visualized under scanning electron microscope (SEM) (JEOL, JSM 840A, Japan).

Results and Discussion

The tablets were prepared in an environment free from organic solvents. From the results it can be stated that plasticizers like PEG-400 at 1.5% and PG at 1% have a significant effect on the film forming property of HPMC. The films formed with HPMC+ PEG400 (1.5%) were free from major defects like cracking, orange peel, picking with good gloss and very slight chipping and splitting occasionally [1-3,9]. In regard to HPMC+PG (1%) the resultant films were free from defects such as roughness, picking, orange peel and cracking, having good gloss and slight chipping. Uniformity in tablet weight gain and thickness of the film coat data obtained from cast film measurements are supportive for elegant film formation. The quality of aqueous film coat or the plasticizer efficiency in case of PEG-400 is in the order 1.5%> 0.5% > 1.0% > and for PG 1%> 4%> 3%. This preliminary study infers that plasticizer significantly influences the quality of aqueous film coats. The best formulations (F3 and F4) are selected for further trials. Two surfactants of high HLB value namely SLS and Tween-80 were tried for bringing uniformity in the spreading efficiency on the substrate surface. It was found out that among the six formulations containing SLS, F3B (HPMC+PEG 1.5%+SLS 0.3%) yielded the most satisfactory result. The films were found to be free from blistering, blooming, chipping, cracking, picking, orange peel, roughness, splitting with uniform color distribution and good glossy appearance. On the other hand with the six formulations of Tween-80, F4E (HPMC+PG1.0%+Tween-80 0.3%) yielded the most satisfactory result. The films were found to be free from blistering, chipping, cracking, picking, orange peel, roughness, splitting with slight blooming, uniform color distribution and good glossy appearance. The quality of aqueous film coat or the surfactant efficiency in case of SLS+PEG-400 is in the order 0.3%< 0.5%< 0.1% and SLS+PG is in the order 0.5%< 0.1%< 0.3%. In case of Tween-80+PEG-400 the order is 0.3%< 0.5%< 0.1% and Tween-80+PG is in the order 0.3%< 0.1%< 0.5%. From this study it may be concluded that surfactants of high hydrophilic nature might be useful in improving the film coating liquid properties to achieve better spreading and resulting in better quality film coats.

Evaluatory parameters of the coated tablets like thickness, weight, diametral hardness, and friability were found to be within the normal limits as stated in Table 7.

The total disintegration time of all the selected tablets was found to be within 2.5 min (F4B) to 3.5 min compared to the uncoated 2.33 min in 0.1(N) HCl. This suggests that there is no abnormality for the drug to disintegrate in its specified environment.

During preformulation study, FTIR (Fourier Transform Infrared) spectra of the pure Met-HCl (Figure 1a) and in its combination with polymer (HPMC 5cPs) under study (Figure 1b) were observed.

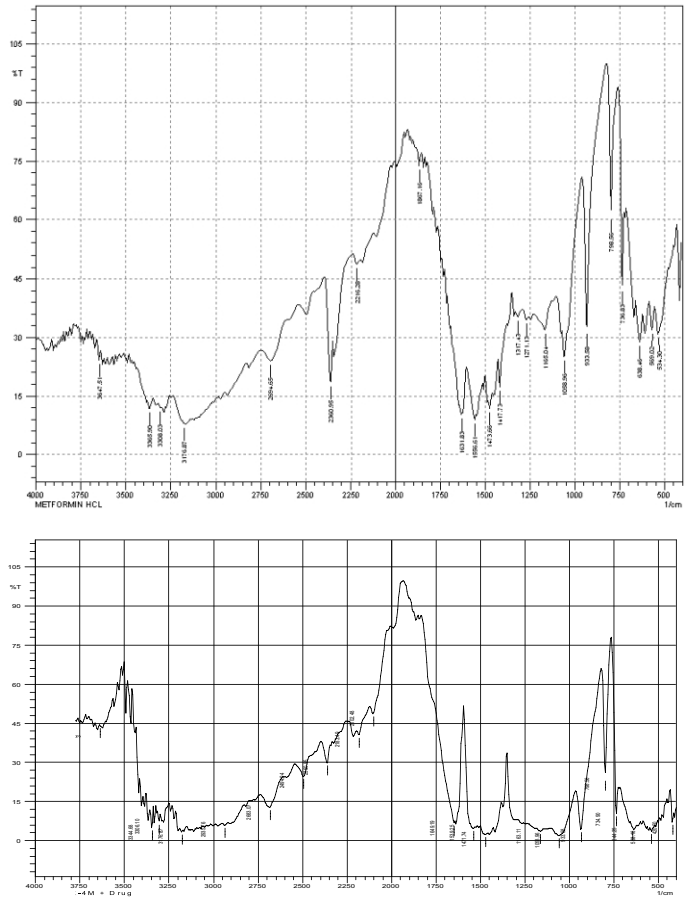

Figure 1. FTIR Spectra of (a) pure Met-HCl (top) and (b) Met-HCl+ HPMC 5cPs (bottom)

It shows C-H alkane stretch at values of 2950 (pure Met-HCl), 2985.76 (Met-HCl+HPMC 5CPS).-NH at 3365.90 (pure Met-HCl), 33.44.68cm-1 (Met-HCl+HPMC 5CPS). For –C=N the values were 1473.66 (pure Met-HCl) and 1471.74cm-1 (Met-HCl+HPMC 5CPS). Major frequencies of functional groups of pure drug remained unchanged in presence of the polymer with other additives. Hence chances of less possible major interaction between the drug and the polymers can be concluded.

The *in vitro* release data of all formulations were fitted in zero order and the rate constants and correlation coefficient were compared to get a trend in the release pattern of the drug from the formulations. From Figure 2, it is evident that the selected batches F3B and F4E predominantly shows a zero order profile releasing the Met-HCl within 1.5h which eventually satisfies the percentage release.

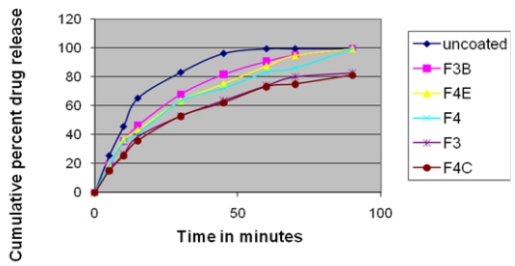

Figure 2. Cumulative percent drug release profiles of coated and uncoated formulations of Met-HCl in PB-6.8

The initial bursting effect of the film coats was obtained in between a time span of 5 min and leaching of the API was observed. The cumulative percent release within 5 min after examination was found out to be in the order F3B>F4E>F4>F3>F4C which suggests the proper functioning of the films.

SEM study further confirmed the proper erosion and diffusion mechanisms to be operative during drug release from the optimized batch of HPMC 5cPs coated Met-HCl tablet (F3B). SEM photomicrographs of the tablets at different time intervals after the dissolution experiment showed that tablets were intact and pores had formed throughout the surface (Figure 3). Photomicrographs from SEM at definite time intervals 0 min, 30 min, (A, B) revealed pores with increasing diameter. The photomicrographs also revealed formation of gelling structure (C) indicating the possibility of swelling and eroding of the tablets

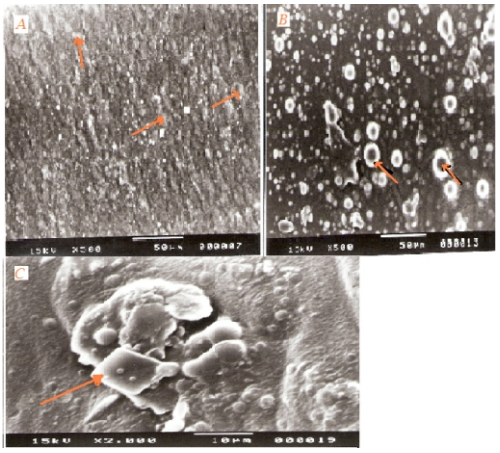

Figure 3. Scanning Electron (SEM) photomicrographs of HPMC 5cPs coated MET-HCL tablets (F3B) showing surface morphology after 0 h (A, 500×), 30 min (B, 500×), 30 min (C, 2000×) of dissolution study (In A and B arrow indicates the formation of pores on coated surface, C indicates eruption and leaching of drug).

Conclusion

In conclusion, tablet coating films made of HPMC 5cPs with the addition of PEG at 1.5% and SLS at 0.3% and films made of HPMC 5cPs with PG at 1% and Tween-80 at 0.3% could be considered as an elegant film forming formulation for solving different coating problems generally faced in an industrial scale. The film coating formulations were entirely prepared in an aqueous environment avoiding the environmental unfriendly toxic hazards accompanied with organic solvents. These optimized formulations could be further developed in an industrial scale for the purpose of coating enteric release formulations for those drugs whose integrity needs to be protected from sunlight, oxidations, moisture, thermolability and foreign microbial attack. The concept of Rx to OTC switch strategy for metformin hydrochoride can be eventually satisfied by the use of such selected formulations for the purpose of coating.

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Conflict of interest

The authors declared no competing interests.

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