Formulation and Evaluation of Press Coated Tablets for Pulsatile Drug Delivery Using Hydrophilic and Hydrophobic Polymers

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The aim of present investigation was to develop press coated tablet for pulsatile drug delivery of ketoprofen using hydrophilic and hydrophobic polymers. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of rheumatoid arthritis. The press coated tablets containing ketoprofen in the inner core was formulated with an outer shell by different weight ratio of hydrophobic polymer (micronized ethyl cellulose powder) and hydrophilic polymers (glycinemax husk or sodium alginate). The release profile of press coated tablet exhibited a lag time followed by burst release, in which outer shell ruptured into two halves. Authors also investigated factors influencing on lag time such as particle size and viscosity of ethyl cellulose, outer coating weight and paddle rpm. The surface morphology of the tablet was examined by a scanning electron microscopy. Differential scanning calorimeter and Fourier transformed infrared spectroscopy study showed compatibility between ketoprofen and coating material.

Key words press coated tablet; ketoprofen; lag time; time-controlled disintegration

Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. These systems are beneficial for the drugs having chronopharmacological behaviour (where night time dosing is required), first-pass effect and having specific site of absorption in gastro intestinal tract (GIT). From the viewpoint of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable.[1)] Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system.[2)] Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs.[3)] Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and hypercholesterolemia. The pathophysiology of arthritis and patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day.[4)]

A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration.[4,5)] This novel system is not only rate controlled but is also time controlled. The dry-coated tablets were prepared by a direct compression method. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture.[6)]

There are various problems with pH dependent drug delivery; however the pH in the gastrointestinal tract varies between and within individuals.[7—9)] It is affected by diet and disease.[10)] During acute stage of inflammatory bowel disease colonic pH has been found to be significantly lower than normal.[11)] In ulcerative colitis pH values 2.3—4.7 have been measured in the proximal parts of the colon.[12)]

The purpose of this study was to develop press coated tablets for pulsatile drug delivery of ketoprofen. The oral press coated tablet was developed to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. Press-coated tablet containing ketoprofen and other excipients in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer (micronized ethylcellulose powder) and hydrophilic polymers (glycinemax husk, sodium alginate). Ethylcellulose (EC) is a well-known water-insoluble polymer that has been used as a rate-controlling membrane to regulate drug release. EC powder with different micronized sizes has been directly compressed to form compact EC in which plastic deformation is the predominant consolidation mechanism.[13)] Glycinemax containing dry matter (DM), crude protein (CP), crude fiber (CF), ether extract (EE), nitrogen free extract (NFE), calcium (Ca), phosphorus (P)[22)] Glycinemax husk has a swelling property[14)] and sodium alginate has an erosion property.[15)] These hydrophilic polymers were responsible for rupturing the outer coat.

There are various parameters which are affecting lag time such as viscosity of EC, paddle rpm, particle size of EC, and over all coating weight. This study also investigate the influence of the type and amount of hydrophilic polymer mixed with micronized EC powder in the outer shell on the time-lag and time-controlled disintegrating or rupturing function of press-coated tablet. The core tablet, prepared by a direct compression method, was designed to disintegrate and dissolve quickly.

Experimental

Materials Ethylcellulose (10 cP, 45 cP, 100 cP) was kindly supplied by Colorcon Asia Pvt. Ltd., Goa, India. Ketoprofen supplied by Shreya Pharmaceuticals, Aurangabad, India. Sodium alginate (molecular weight 216 g/mol, viscosity 150 cP and M/G ratio 0.74) purchased from Loba Chemicals, Mumbai, India. Magnesium stearate was procured from S.D. Fine-Chem. Ltd., Ahmedabad, India; all other ingredients were of analytical grade.

Methods. Preparation of Glycinemax Husk Powder Two kilograms of glycinemax was purchased from local distributor in Shirpur (India). The raw

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material was dried at 400 °C for 12 h in hot air oven. Dried material was crushed immediately in pulverizer and passed through sieve #100 to get fine powder.

Drug Excipients Compatibility Study Sample of pure drug, coating polymer, physical mixture of coating material and drug in (1 : 1) ratio was placed at accelerated stability condition 40±2 °C and 75±5% relative humidity for a period of 3 month. At the end of 3 month samples were evaluated for drug–excipients compatibility using Differential scanning colorimeter (DSC) and Fourier transformed infrared spectroscopy (FT-IR).

Differential Scanning Colorimeter: Thermograms of pure ketoprofen, EC, sodium alginate, glycinemax husk, physical mixture of coating material and drug (1 : 1), and mixture of optimized formulations were obtained using DSC (Mettler Toledo DSC 822e, Japan) at a scanning rate of 10 °C/min conducted over a temperature range 30—400 °C.

Fourier Transformed Infrared Spectroscopy: FT-IR spectra of drug, mixture of optimized formulation, physical mixture of coating material and drug (1 : 1) and core tablet mixture were recorded with a FT-IR spectrophotometer (Shimadzu Corporation, Japan, 8400s) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1 : 100 and pressed using a hydrostatic press (Kimaya Engineers, Mumbai, India) at a pressure of 10 tons for 5 min. The disc was placed in the sample holder and scanned from 4000 to 500 cm^{-1} at a resolution of 1 cm^{-1}.

Precompression Parameters of Coating Powder Blend and Core Tablet Powder Blend Coating powder blend and core tablet powder blend was evaluated for various precompression parameters such as angle of repose, loose bulk density, tapped bulk density, Hausner's ratio and compressibility index (Table 1).

Preparation of Ketoprofen Core Tablet The core tablets of ketoprofen were prepared by direct compression technique. Each core tablet contained 100 mg of ketoprofen, 2 mg of croscarmellose sodium, and 2 mg of magnesium stearate. Firstly ketoprofen and croscarmellose sodium were mixed, magnesium stearate was added and mixed thoroughly. Powder was compressed into 7-mm flat tablets with use of a single station tablet machine (Cadmach SSF3, Ahemdabad, India). The core tablets were evaluated for tensile strength, thickness, content uniformity, friability and disintegration.

Preparation of Compression-Coated Tablets On compliance with the above mentioned tests, the core tablets were compression coated with different weight ratios (w/w) of EC/glycinemax and EC/sodium alginate mixtures. Initially 50% of the coat powder was placed in the die cavity then, the core tablet was carefully positioned at the center of the die cavity which was filled with the remainder of the coat powder. It was then compressed around the core tablet by using 10-mm round, flat, plain punches at pressure of 175 kg/cm^2. Formulations of press coated tablet were shown in Table 2.

Drug Content of Core Tablet Tablets were finely powdered and quantity of the powder equivalent to 10 mg of ketoprofen was accurately weighed and transferred to volumetric flask containing 100 ml phosphate buffer (pH 6.8) and mixed thoroughly. One milliliter of filtrate with suitable dilution was estimated for ketoprofen content at 260 nm using double beam spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Characterization of Core and Press Coated Tablet The physical properties such as weight variation, tensile strength, thickness, friability, of core tablets and press coated tablets were given in Table 3. All tablet parameters were complied with Pharmacopoeial standards.

Lag Time: Twenty tablets were selected randomly and weighed individually. Calculated average weight and compared the individual tablet weight to the average.

Friability Test: Friability was performed by using Roche friabilator; normally preweighed 20 tablets were placed in the plastic chamber of friabilator and then operated for 100 revolutions. Tablets dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed.

$$F(\%) = \frac{\text{initial wt.} - \text{final wt.}}{\text{initial wt.}} \times 100 \quad (1)$$

Table 2. Formulations of Press Coated Tablet

Formulations	Variable specification	Composition			Total weight (mg)
		EC	GH	NA	
Evaluation of ethocel viscosity					
F1	Ethocel 10 cP	300	—	—	402±2.1
F2	Ethocel 45 cP	300	—	—	401±2.5
F3	Ethocel 100 cP	300	—	—	400±2.9
Evaluation of hydrophilic polymers concentration					
F4	20%	240	60	—	400±1.9
F5	30%	210	90	—	403±1.8
F6	40%	180	120	—	402±3.2
F7	10%	270	—	30	401±3.5
F8	20%	240	—	60	401±3.9
F9	30%	210	—	90	403±2.1
Evaluation of coating weight					
F10	20%	480	120	—	700±2.1

EC, ethylcellulose (Ethocel); GH, glycinemax husk; NA, sodium alginate.

Table 3. Evaluation of Core and Press Coated

Formulations	Thickness (mm)	Friability (%)	Tensile strength (MPa)	Lag time (h)
Core tablet	2.1±0.005	0.21	3.14±0.13	—
F1	4.12±0.01	0.07	4.43±0.34	22
F2	4.85±0.005	0.09	3.27±0.32	13
F3	5.04±0.01	0.06	2.72±0.22	0.5
F4	4.35±0.057	0.16	3.48±0.47	6
F5	4.38±0.01	0.12	3.95±0.26	3
F6	4.39±0.01	0.19	3.25±0.59	2
F7	4.09±0.005	0.09	3.94±0.46	6
F8	4.27±0.005	0.10	4.40±0.06	3
F9	4.24±0.01	0.11	4.40±0.16	2
F10	7.45±0.005	0.10	2.83±0.12	10

All values are mean±S.D. (n=3).

Table 1. Precompression Parameters of Core Tablet Blend and Coating Materials Blend

Formulation code	Parameters				
	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio (H_R)	Compressibility index (%)
Core tablet blend	39.41±0.41	0.45±0.01	0.51±0.044	1.13±0.023	11.76±0.89
F1	33.25±0.21	0.33±0.021	0.38±0.028	1.15±0.16	13.15±0.49
F2	33.19±0.18	0.34±0.014	0.41±0.012	1.201±0.023	17.03±0.65
F3	37.31±0.24	0.35±0.091	0.42±0.023	1.2±0.141	16.66±0.55
F4	34.21±0.34	0.33±0.023	0.391±0.04	1.181±0.16	15.64±0.48
F5	33.01±0.45	0.32±0.014	0.38±0.044	1.181±0.16	15.85±0.49
F6	33.45±0.52	0.34±0.018	0.38±0.028	1.11±0.16	10.52±0.44
F7	32.89±0.39	0.36±0.023	0.42±0.012	1.16±0.023	14.28±0.49
F8	33.11±0.32	0.35±0.019	0.41±0.023	1.28±0.089	14.63±0.61
F9	32.99±0.41	0.37±0.018	0.44±0.049	1.189±0.16	15.90±0.45
F10	31.41±0.3	0.38±0.023	0.44±0.044	1.07±0.16	13.63±0.81

All values are mean±S.D. (n=3).

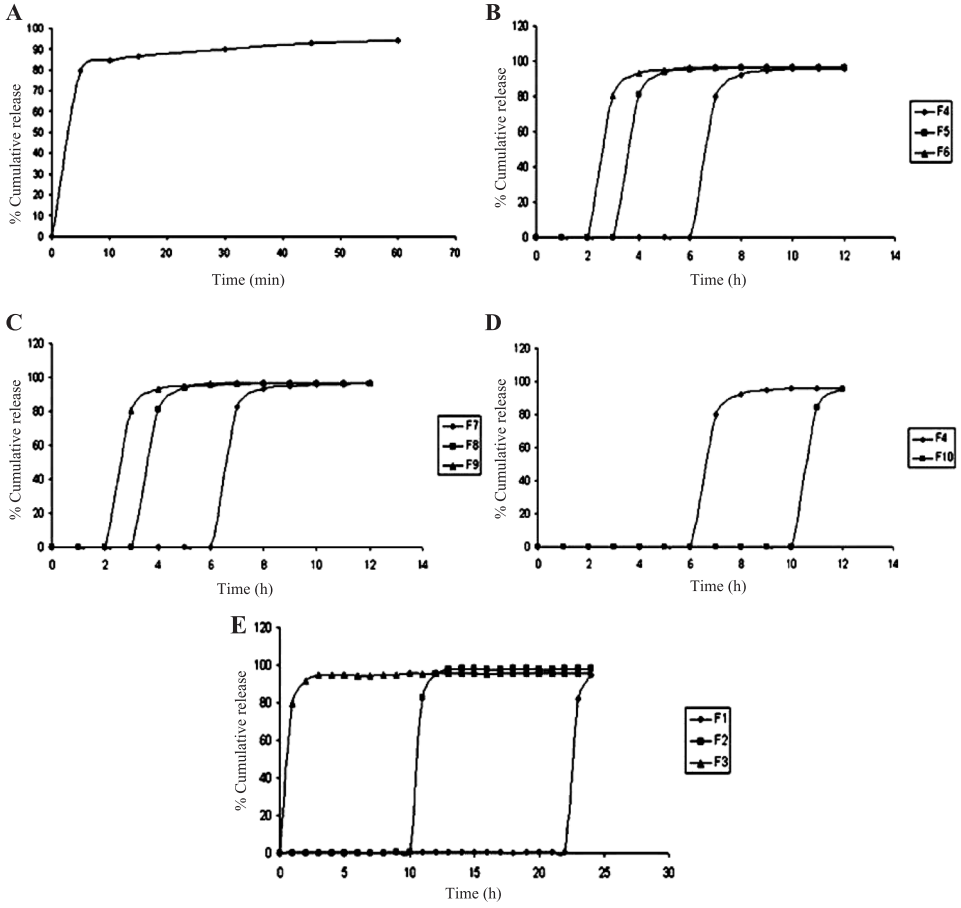

Fig. 1. (A) Dissolution Profile of Immediate Release Core Tablet, (B) Dissolution Profile of Batch F4, F5, and F6, (C) Dissolution Profile of Batch F7, F8, and F9, (D) Dissolution Profile of Batch F4 and F10, (E) Dissolution Profile of Batch F1, F2, and F3

Measurement of Tensile Strength: The tablets were subjected to the diametral tensile test using a Ubique tensile tester by placing tablet between upper and lower platen (60001; Ubique Enterprises, Pune, India). The test was performed by applying a diametrical load, measuring the maximum load F at the tablet fracture and calculating the radial tensile strength T using the following equation

$$T = \frac{2F}{\pi DH} \quad (2)$$

Where D is the tablet diameter and H is the tablet thickness.[16)]

Dissolution Study of Core and Press Coated Tablet Dissolution of ketoprofen tablets were performed in a USP dissolution tester, paddle method (Electrolab TDT-08L Plus, Dissolution tester USP Mumbai, India), under stirring at 100 rpm. The dissolution media consisted of 900 ml of phosphate buffer (pH 6.8) at 37±0.5 °C. Samples were withdrawn after every 5 and 60 min for core and press coated tablet respectively, then filtered and analyzed at 260 nm using UV spectrophotometer. An equivalent volume of temperature equilibrated fresh buffer was replaced following the removal of each sample[17)] (Fig. 1).

Factors Affecting on Lag Time The parameters such as viscosity of EC, paddle rpm, particle size of EC, over all coating weight, and concentration of hydrophilic polymer were studied and evaluated in the form of lag time.

Surface Morphology Study The surface morphology of coating layer and core tablet was examined by a scanning electron microscope (JSM-6390 LV, Jeol, U.S.A.). The samples were mounted onto the stages prior to coating with gold to a thickness of about 30 nm under vacuum, then observed with a scanning electron microscope. Electron micrographs were obtained at an acceleration voltage of 5 kV.[18)]

Results and Discussion

Drug Excipients Compatibility Study. Differential Scanning Colorimeter Fourier Transformed Infrared Spectroscopy: FT-IR spectra of ketoprofen, physical mixture (EC 10 cP: glycinemax husk: ketoprofen) and physical mixture (EC 10 cP: sodium alginate: ketoprofen), shown in Fig. 2. The characteristic absorption peaks of ketoprofen was found at 3020 cm^{-1} (C–H stretching of aromatic ring), 2970 cm^{-1} (C–H stretching of CH_3 group), 1695 cm^{-1} (C=O stretching of acid), 1655 cm^{-1} (C=O stretching of ketone), 1595 cm^{-1} (C=C stretching of aromatic ring), 860 cm^{-1} (C–H deformation of aromatic ring). In physical mixture the intensity of ketoprofen peak was reduced, due to presence of other excipients.

The DSC thermogram shows that the sharp endothermic peak at 94.19 °C corresponding to the melting point of ketoprofen and the endothermic peak at 92.13 °C and 89.66 °C of physical mixture (EC 10 cP: glycinemax husk: ketoprofen) and physical mixture (EC 10 cP: sodium alginate: ketoprofen) respectively, which shows that there is no interaction between polymers and drug (Fig. 3).

Precompression Parameters of Coating Powder and Core Tablet Powder Blend The results of angle of repose, bulk density, tapped density and compressibility index indicates that powder blend has passable flow property with good compressibility and suitable for direct compression method (Table 1).

Characterization of Core and Press Coated Tablet

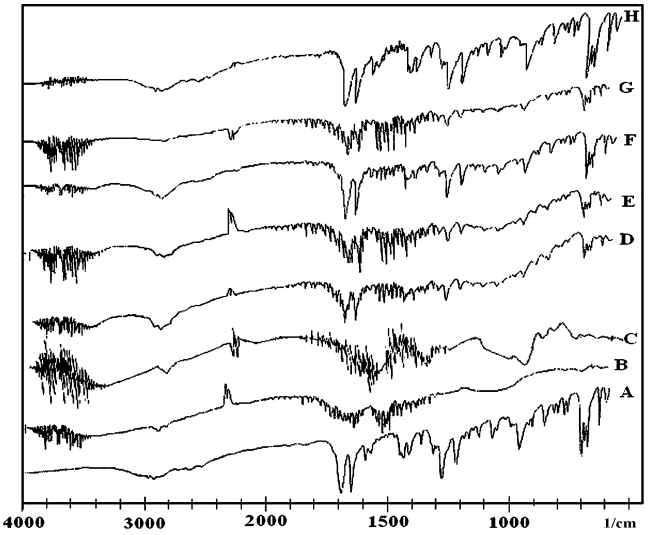

Fig. 2. FT-IR Spectra of Ketoprofen (A), Glycinemax Husk (B), Sodium Alginate (C), Physical Mixture of Ethocel 10 cP, Glycinemax Husk and Drug (D), Physical Mixture of Ethocel 10 cP, Sodium Alginate and Drug (E), Optimized Batch F4 (F), Optimized Batch F7 (G), Core Tablet Mixture (H)

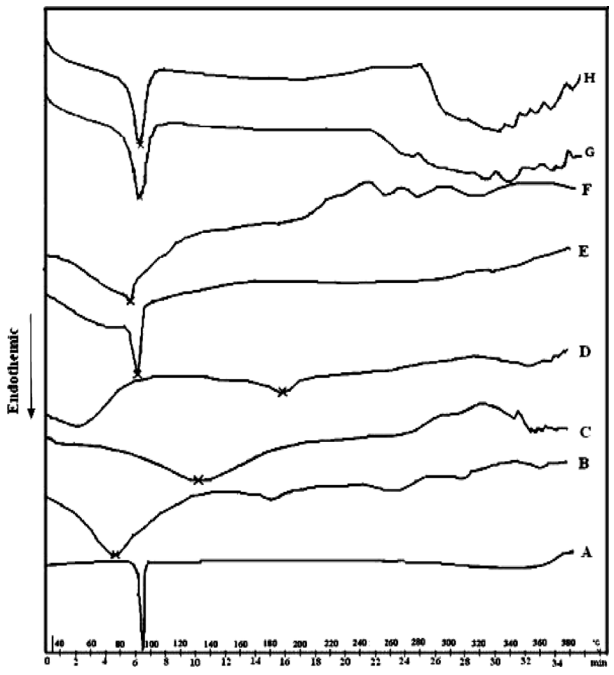

Fig. 3. Thermograms of Ketoprofen (A), Glycinemax Husk (B), Sodium Alginate (C), Ethyl Cellulose 10 cP (D), Physical Mixture of Glycinemax Husk, Ethyl Cellulose 10 cP and Drug (E), Physical Mixture of Sodium Alginate, Ethyl Cellulose 10 cP and Drug (F), Optimized Formulation Batch F4 (G), Optimized Formulation Batch F7 (H)

Weight variation was found to be within USP limit. The tensile strength of batch F1 to F10 was found to be within the range 2.72 to 4.43 MPa. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. Drug content was observed within the range 99—102%.

Factors Affecting on Lag Time Effect of EC Particle Size on Lag Time: Particle size of EC greatly affects the lag time. EC of different particle size ($<90\,\mu$m and $>600\,\mu$m) used in optimized formulation (F4). The result indicates that,

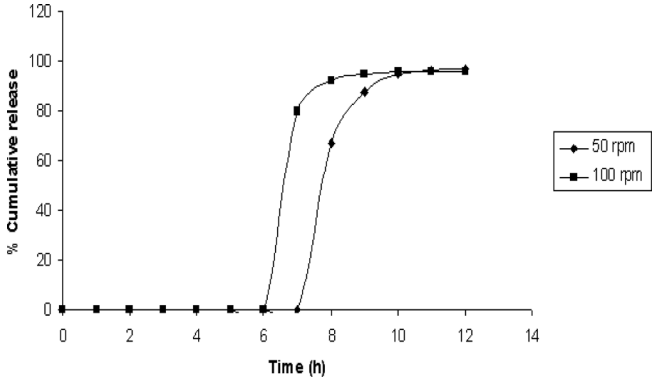

Fig. 4. Release Profile of Formulation F4 under Different rpm

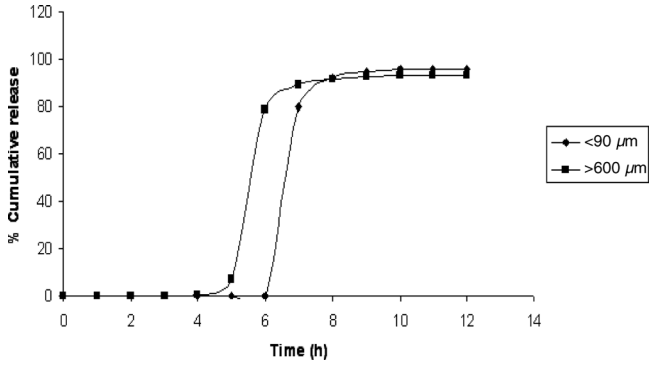

Fig. 5. Release Profile of Ketoprofen from Compression Coated Tablet Using Different Particle Size of Ethyl Cellulose 10 cP

the porosity is proportional to the particle size of coating polymer (EC). Increase in particle size of EC leads to higher penetration of dissolution media in press coated tablet (Fig. 5).

Effect of EC Viscosity on Lag Time: The release profile of ketoprofen from press coated tablets (Fig. 1E), coated with different viscosity grades of EC (10 cP, 45 cP, 100 cP). As increases in the viscosity of EC, lag time of formulations decreases. It was due to the viscosity of EC proportional to the % porosity of coating.[19]

Effect of Paddle rpm on Lag Time: To investigate the effect of rpm on lag time, dissolution study of optimized formulation (F4) was carried out at 50 and 100 rpm. The result indicates that increase in the paddle rpm decreases lag time. It may be due to the paddle rpm proportional to the penetration of dissolution media in coating (Fig. 4).[20,21]

Effect of Outer Coating Weight on Lag Time: Formulations F4 and F10 containing different outer coating weight 300 and 600 mg respectively. The result indicates that coating weight proportional to the lag time. The larger amount of coating material produces tablets with higher thickness and longer path for buffer media to penetrate into the core (Fig. 1D).

Effect of Hydrophilic Polymers Concentration on Lag Time: The hydrophilic polymers used in this drug delivery having ability to modulate the lag time. Glycinemax husk and sodium alginate having swelling and erosion properties respectively. Amount of husk and sodium alginate increased in formulation leads to faster swelling and erosion which is responsible for breakdown of outer coating (Figs. 1B, C).

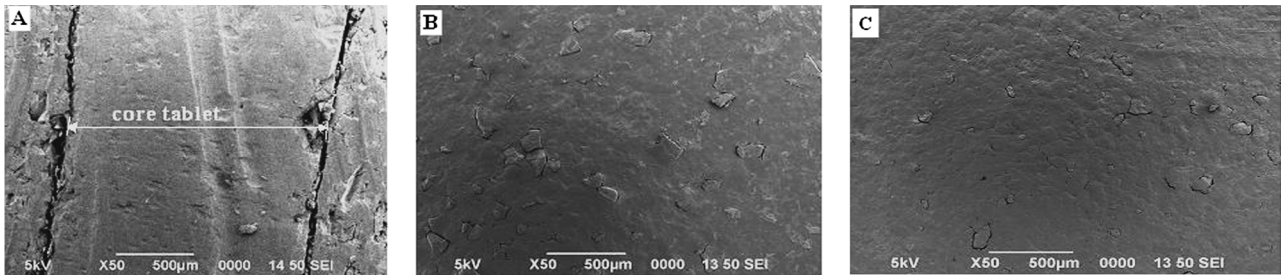

Fig. 6. Scanning Electron Photomicrographs of Cross Section of Press Coated Tablet (A), Press Coated Tablet of Formulation F4 (B), Press Coated Tablet of Formulation F7 (C)

Surface Morphology Study The morphological evaluation of press coated tablet was performed by scanning electron microscopy. The surface morphology of optimized formulation F4 (Fig. 6B), F7 (Fig. 6C), and differentiate core tablet and compression coating layer (Fig. 6A) was given. Small pores or fractures were found on coating surface which may be due to hydrophilic polymer used in combination with EC.

Stability Study FT-IR data shows that intensity of ketoprofen peak was reduced in mixture of optimized formulation (F4, F7), it may be due to formulation excipients. No change was observed in IR spectra of immediate release core tablet (Fig. 2). DSC study shows that there was no change in endothermic peak of ketoprofen in optimized formulations. Also there was no change on lag time of optimized formulations.

Drug Release Mechanisms of Press Coated Tablets The release profile of compression coated tablet exhibited lag time followed by burst release, in which outer shell break into two halves. Release of drugs from the compression-coated tablet follows three consecutive steps: 1) penetration of dissolution media into the compressed coated tablet 2) swelling or erosion of hydrophilic polymer 3) breakdown of outer coating into two halves due to swelling or erosion of hydrophilic polymer used in coating.

Conclusion

The lag time and time-controlled release behavior of ketoprofen from press-coated tablets could be modulated by changing the particle sizes of EC powders in outer coating, viscosity of EC, paddle rpm, coating weight, and hydrophilic polymers concentration. Formulations F4 and F7 compression coated tablets achieve a burst release after 6 h lag time which is applicable pulsatile drug delivery of ketoprofen for rheumatoid arthritis.

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