Research Paper

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Evaluation of Ethocel® Premium Ethylcellulose Ether Derivatives with Different Molecular Weights as Controlled-release Matrix Forming Functional Polymers for Ibuprofen

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This research work was promoted by the desire to investigate and compare the potentials of conventional granular Ethocel® Premium and Ethocel® Standard FP Premium (the latest in the ethylcellulose ether family) as controlled-release (CR) hydrophobic matrix forming functional polymers for ibuprofen (IBF), a sparingly water-soluble, anti-inflammatory agent. IBF- Ethocel® CR matrix tablets were prepared by direct compression as well as by wet granulation methods. The influence of several parameters such as polymer type, molecular weight (viscosity grade), and particle size; drug-to-polymer (D:P) ratio; and preparation methodology of the matrices on the physical characteristics of the granulations as well as the tablets and IBF release rates from the matrix tablets were investigated. The dissolution equivalency of the release profiles from the formulations investigation were determined making the use of f_2-metric technique by fitting the release profiles data into the f_2-metric equation using a computer program. Granular Ethocel® polymers with lower viscosity grades demonstrated greater compressibility and lower release rates than those with higher viscosity grades. Ethocel® standard FP Premium polymers exhibited greater efficiency in controlling the release of IBF from the matrices as compared to the granular conventional Ethocel® polymers. Moreover, polymer level and particle size, rather than viscosity grade of the polymers, were found to be determining factors in controlling the drug release rates. Furthermore, matrices prepared by wet granulation showed more efficient control to retard the drug release rates than those prepared by direct compression method.

Key words: IBF, Ethocel® polymers, matrix tablets, preparation methodology, controlled-release matrix

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Introduction

In recent years the use of matrix forming functional polymers has gained momentum in the pharmaceutical industry with regard to prolonged-release formulations. Ethylcellulose is an inert, hydrophobic polymer (Kumar and Banker, 1993) and has been extensively used as a pharmaceutical vehicle in a number of dosage forms as binder, film forming agent (Rowe, 1986) and as a coating material (Palmieri and Wehrle, 1997; Lin *et al*., 2001; Ymada *et al*., 2001). It has also been used as a matrix forming material (Shaikh *et al*., 1987, 1987a; Shlieout and Zessin, 1996).

Ethocel® Premium ethylcellulose ether polymers are derived from ethylcellulose. These are organosoluble thermoplastics that have been used in pharmaceuticals since their commercial introduction in 1930's (Ethocel®, 1996). Until recently, Ethocel® Premium products have been available only in varying viscosity grades, physically granular in nature, with average particle size greater than 250μm (Ethocel®, 1996). Usually, these polymers require to be dissolved in organic solvent during the preparation of dosage forms, however, the environmental issues are making these processes less tolerable and more expensive. To avoid this, the Dow Chemical Co. has, very recently, introduced Ethocel® Standard FP Premium polymers (Ethocel® Standard 7, 10 and 100FP, Premium) which are claimed to be very finely milled form of its Ethocel® Premium products with improved physical form and use in direct compression controlled-release (CR) matrix applications. Therefore, this research work was conducted to investigate the potentials of the conventional granular Ethocel® and Ethocel® Standard FP Premium as direct compression CR matrix forming functional polymers; the effect of preparation methodology (direct compression and wet granulation) of tablets and the effect of different viscosity grades (molecular weights), and drug-to-polymer (D:P) ratios of the granular Ethocel® vs. Ethocel® Standard FP Premium polymers on the tablet characteristics and IBF release rates from the matrix tablets.

Materials and Methods

Materials: Ibuprofen (IBF) was purchased from Xin Hua Pharmaceutical Factory (Shandong, China), Ethocel® Standard Premium and Ethocel® Standard FP Premium polymers with different viscosity grades (Table 1) were obtained as gratis supply from the Dow Chemical Co. (Midland, USA). Lactose and magnesium stearate (Shanghai Reagent Factory No. 2, Shanghai, China) and all other reagents used were analytical grade.

Tablet Formulation: 300mg IBF-Ethocel® tablets, containing 200mg IBF, were formulated at D:P ratios of 10:1, 10:2 and 10:3. Lactose was used as an excipient and magnesiumstearate (0.5% w/w) as a lubricating agent throughout the formulations. The granulating liquid used was a hydro-alcoholic solution (C_2H_5OH/H_2O, 30:70 v/v).

Tablet Preparation

Direct Compression Method: IBF and the respective polymer at different D:P ratios were mixed with the excipient, initially by adding and mixing geometrically using a mortar and pestle; then passing each powder mixture thricely through a # 30 mesh screen in order to get thorough mixing of the constituents. Finally, 0.5% (w/w) magnesium stearate, as a lubricant, was added and each of the resulting mixture was again passed twicely through the same mesh screen. Each of the powder mixtures was directly compressed into tablets on a single punch tableting machine (Shanghai Mechanical Equipment Factory, Shanghai, China) using flat-faced beveled-edges tooling with 11mm diameter. The target tablet weight was 300mg and tablet hardness was between 6 and 7kg (Khan and Zhu, 1998).

Wet Granulation Method: Physical mixing of the components was performed as described above, however magnesium stearate was not added at this stage. Each mixture was moistened by aspersion, using a hydroalcoholic (C_2H_5OH/H_2O 30/70 v/v) solution, and kneaded continuously until the subjective end point i.e. suitable consistency of the mixture. Wet milling was performed by passing the wet masses through a # 8 mesh screen by hand. The wet granulations were placed in Teflon-coated trays in beds with a thickness of about 0.5cm and were dried in a hot air conventional oven at 45°C until moisture content between 0.5 and 1.0% was achieved. The dry granulations were dry milled using a # 18 mesh sieve and finally lubricated with 0.5% w/w magnesium stearate. The granulations were compressed into tablets as described above.

Properties of the Granulations: Physical properties of the granulations were evaluated using a number of simple techniques. The apparent and tap densities of the granulations were determined by weight/volume relationship. The compressibility index (I) was calculated from the apparent and tap densities using the following equation (Easterbrook, 1998)

$$I = [1 - V_a / V_t] \times 100$$

where V_a is the apparent density and V_t is the tapped density. I can be used as a rough indication of the flow properties of a material; where I values of $< 15\%$ are indicative of good flow characteristics and $> 25\%$ generally indicate poor flowability. Moreover, the angle of repose (Φ) were also measured using simple geometric technique.

Table 1: Physical properties of Ethocel® Standard Premium and Ethocel® Standard FP Premium polymers (Ethocel®, 1996)

Standard Ethocel® Premium	Average particle size (μm)	Viscosity* (cps)
7 cp	310	7
7 FP	9.7	7
10 cp	375	10
10 FP	6.1	10
20 cp	----	20
45 cp	----	45
100 cp	465	100
100 FP	41	100

* Solution viscosity of a 5 % (w/w) polymer in 80/20 toluene/alcohol at 25

Table 2: Effect of polymer type, D:P ratios, and viscosity grade on properties of the granulations

D:P Ratio	Polymer (Ethocel®)	Apparent Density (g cm^{-3})	Tap Density (g cm^{-3})	I (%)	Repose Angle	Recovery (%)
10:1		0.80	0.89	10.1	29	49.67 ± 1.92
10:2	7 cp	0.82	0.91	9.9	31	49.50 ± 2.35
10:3		0.83	0.90	7.8	31	49.62 ± 2.59
10:1		0.92	0.97	5.2	27	49.73 ± 0.09
10:2	7 FP	0.93	0.97	4.1	26	49.84 ± 1.87
10:3		0.93	0.98	5.1	29	49.59 ± 2.18
10:1		0.76	0.91	16.5	34	49.21 ± 2.69
10:2	10cp	077	0.91	15.4	32	49.44 ± 2.37
10:3		0.79	0.92	14.1	33	49.39 ± 2.89
10:1		0.93	0.98	5.1	25	49.91 ± 2.03
10:2	10FP	0.94	0.99	5.1	25	50.04 ± 3.10
10:3		0.95	0.99	4.0	27	49.83 ± 2.94
10:1		0.74	0.88	15.9	33	48.99 ± 2.37
10:2	20cp	0.75	0.89	15.7	33	49.82 ± 1.98
10:3		0.79	0.92	14.0	30	49.31 ± 2.67
10:1		0.72	0.87	17.2	35	48.67 ± 2.88
10:2	45cp	0.74	0.88	15.9	33	49.31 ± 2.51
10:3		0.75	0.90	16.7	37	49.68 ± 1.92
10:1		0.67	0.88	23.9	36	48.91 ± 3.08
10:2	100cp	0.70	0.88	20.5	34	49.20 ± 2.89
10:3		0.72	0.90	20.0	38	49.01 ± 3.38
10:1		0.86	0.95	9.5	29	49.59 ± 1.93
10:2	100FP	0.87	0.97	10.3	32	49.73 ± 2.17
10:3		0.86	0.97	11.3	30	49.81 ± 2.36

Table 3: f_2-metric values for the determination of equivalency between the release profiles from granular Ethocel® and Ethocel® FP polymer matrices as function of D:P ratio and viscosity grade of the polymers

D:P ratio	Gr.* Ethocel® using Ethocel® 7cp as reference	f_2-metric values	Gr.*Ethocel®vs. Ethocel® FP Reference / Test	f_2-metric values
10:1		53.2503		41.5345
10:2	Ethocel® 7cp/Ethocel®10 cp	49.3385	Ethocel® 7cp/Ethocel® 7 FP	40.5641
10:3		35.8490		45.4498
10:1		49.9490		28.2113
10:2	Ethocel® 7cp/Ethocel®20 cp	45.4243	Ethocel® 10cp/Ethocel® 10 FP	26.3842
10:3		52.4309		27.3842
10:1		39.8738		42.5796
10:2	Ethocel® 7cp/Ethocel®45 cp	37.7040	Ethocel® 100cp/Ethocel® 100FP	24.7618
10:3		46.2485		23.8480
10:1		35.6744		
10:2	Ethocel® 7cp/Ethocel®100 cp	38.2114	---------	--------
10:3		43.7651		

Gr* = Granular

Particle Size Distribution (PSD): PSD of the granulations was also determined. The amount of the material retained on the Chinese Standard Sieves of 20, 40, 60, 80, 100, and < 100 (fines over pan) mesh sieves, after shaking manually for about 5 min., were noted as the average of the three determinations.

IBF Content Determination Test: Following the established method (Khan and Zhu, 1998), the required amount of respective granulation or crushed tablet powders equivalent to 10mg of IBF was dissolved in 100ml of hydro-alcoholic solvent. Into this 3 drops of 1M NaOH was added in order to improve the solubility. Samples of 5ml were filtered (0.45μm) and analyzed spectrophotometrically (752-C, The 3rd Analytical Instruments Factory, Shanghai, China) at 264nm.

Hardness and Friability Tests: Hardness and friability (10 tablets for 15 min. at 20rpm) of the tablets were determined using Erweka TB and Erweka TAP (Heusenstamn, F.R. Germany) apparatuses, respectively. Tablet thickness was also measured using a vernier caliper (GB 1214, Shanghai, China).

***In Vitro* Drug Release Studies:** Drug release studies of the tablets were carried out using USP method 1 (rotating basket) with ZRS-4 Intelligent Dissolution Tester (Tianjin University Radio Factory, Tianjin, China) at a speed of 100rpm. The dissolution medium (pH 6.8; phosphate buffer solution) was thermally maintained at 37 ± 0.1°C. At predetermined time intervals 5ml samples were withdrawn, filtered (0.45 μm) and analyzed spectrophotometrically (752-C) at 264nm. After each sampling, equal volumes of the dissolution medium (maintained at 37 ± 0.1°C) were added as replacement. From the absorbance values the cumulative percentage of IBF released was calculated, using the standard curve for IBF (Khan and Zhu, 1998).

Determination of Dissolution Equivalency: The use of f_2 metric equation (Easterbrook, 1998; Costa, 2001) was made, which has recently been recommended for use by the US FDA when determining the equivalence of dissolution profiles;

$$f_2 = 50\ \mathrm{Log}\{[\ 1 + 1/n\textstyle\sum_{t=1}^{n}(R_t-T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t represent the release profiles data from the reference and test formulations at time 't'. f_2 = 100 when test and reference profiles are identical and decreases as the level of dissimilarity increases. The US FDA has suggested that f_2 values between 50 and 100 constitute identical behavior. f_2 values were computed by linear regression analysis, fitting the release profiles data from the reference and test formulations in the above equation, using a computer

program 'True Basic-Version 2.03' (True Basic Inc., USA).

Results and Discussion

Properties of the Granulations: Table 2 represents the apparent and tap densities, compressibility index, angle of repose percent recovery of IBF for each formulation of this investigation. It can be observed that for a given polymer, the differences in density among 10, 20 and 30% polymer levels were small, nevertheless the densities at higher polymer levels were usually greater (equal in some cases) than the lower Conversely, the compressibility indices (I) decreased in most of the cases as the polymer level increased and were consistent with the good flow properties of the granulations studied. The angle of repose varied from the lowest of 25° for the granulations resulted from 10 and 20% of Ethocel® Standard 10 FP Premium to the highest of 38° for those of the granular Ethocel® Standard 100 cp Premium; with all the remaining granulations having values between these two limits. No well established correlation could be found between the angle of repose, the I values of granulations, and the manners in which the granules actually flowed during tablet preparation.

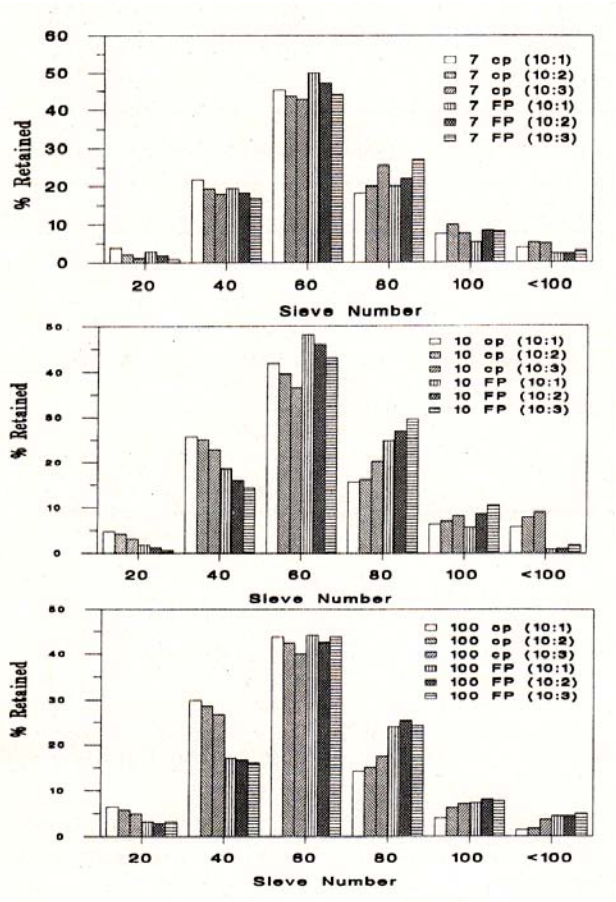

Fig. 1: Effect of polymer type and viscosity grade on particle size distribution of the granulations

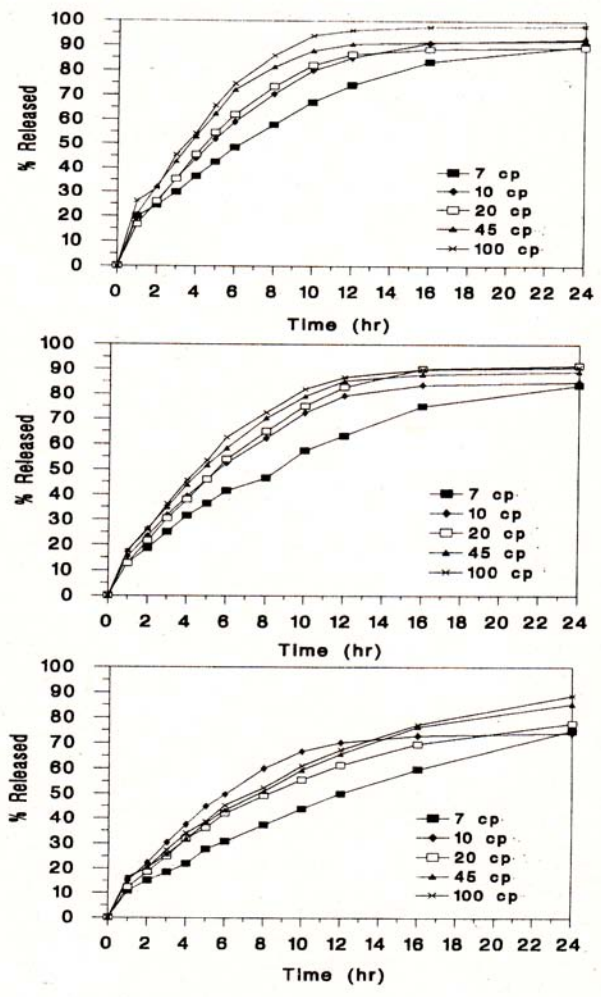

Fig. 2: Release profiles of IBF from Ethocel® matrices with different viscosity grades containing D:P 10:1 (upper), 10:2 (middle), and 10:3 (lower)

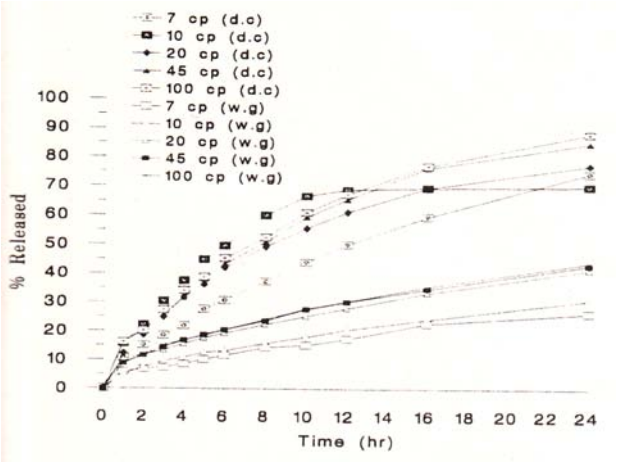

Fig. 3: Release profiles of IBF from directly compresses (d.c) and wet granulated (w.g) IBF-Ethocel® (10:3) matrix tablets

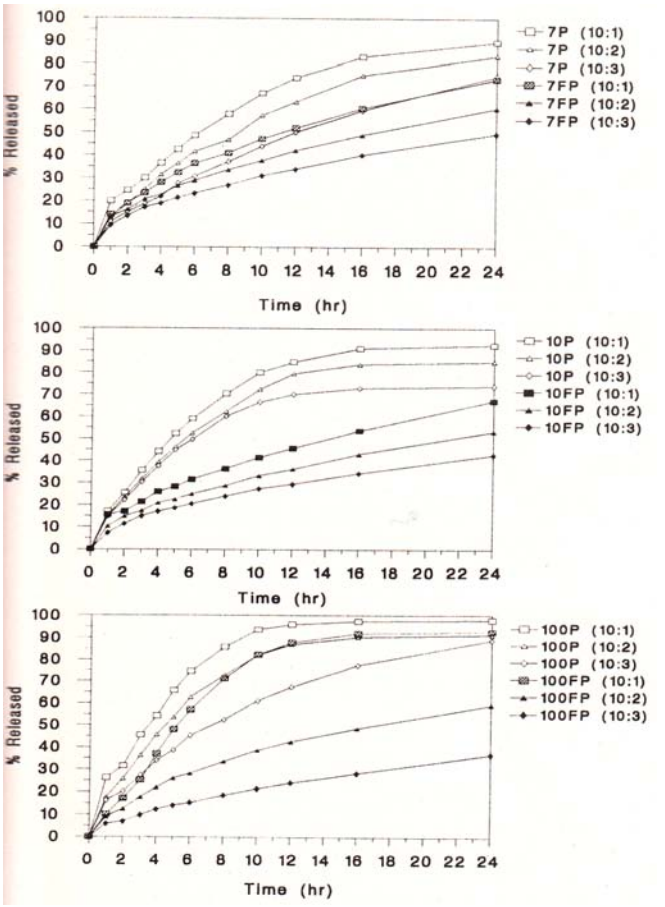

Fig. 4: Release profiles of ibuprofen from Ethocel® Premium (P) and Ethocel® FP premium matrices with different viscosity grade and D:P ratios

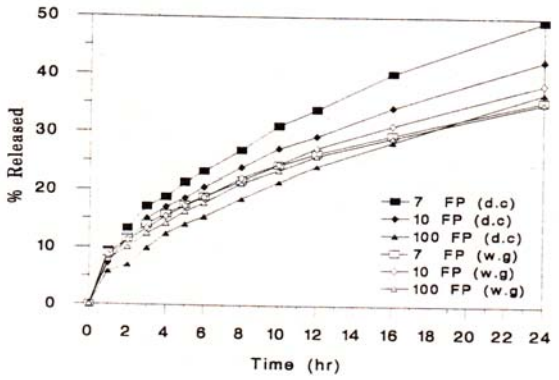

Fig. 5: Release profiles of IBF from directly compressed (d.c) and wet granulated (w.g) IBF-Ethocel® standard FP polymer (10:3) tablets.

Particle size Distribution (PSD): Fig. 1 compares the PSD of granulations obtained from the granular Ethocel® with those of the Ethocel® Standard FP Premium of different viscosity grades and at different polymer levels. It could be observed that the amounts retained on different mesh screens in case of the granular Ethocel® are quiet different than those of Ethocel® Standard FP Premium polymers. Generally, at almost all the polymer levels and viscosity grades, the granular Ethocel® polymers exhibited retention of greater amounts over # 20 and 40 mesh sieves as compared to their respective counterparts of the FP series. Ethocel® 7 and 10 cp produced more fines (portion retained on < 100 mesh sieve) than the corresponding Ethocel® 7 and 10 FP; while in case of Ethocel® 100 cp and 100 FP polymers the reverse was true. The amounts retained on # 100 mesh sieve demonstrated somewhat mixed and diffused patterns of the PSD. In all the formulations, the median of the granulation was lying at # 60 mesh sieve, however, FP polymer resulted in retaining greater amounts of the granulations, both at # 60 and 80 mesh sieves, as compared to the granular Ethocel® polymers at the respective polymer levels. Among the same series of the polymers, it was found that increasing the polymer level from 10 to 30 % caused, with a few exceptions, decrease in the amounts retained over # 20, 40 and 60 mesh sieves and an increase on # 80, 100, and < 100 mesh sieves.

Focusing attention on the impact of the viscosity grade (molecular weight) of the polymers, it was found that polymers with increasing viscosity grades demonstrated the ability of retaining greater amounts over # 20, 40 and < 100 mesh sieves at the respective polymer levels; while a trend of decreasing amounts retention was seen over # 80 and 100 mesh sieves as the polymer viscosity increased. Ethocel® Standard 10 FP polymers was the exception in some cases. A few deviations from the above described trends were also observed in some cases of the Ethocel® 100 cp polymers.

Physical properties of the Tables: The thickness variation measured for all the formulations (n = 10) was excellent in all the cases. The best values were shown by the tablets containing Ethocel® Standard FP Premium polymers prepared by the wet granulation method, with almost 0% RSD (RSD = SD/mean × 100), followed by wet granulated tablets

with the granular Ethocel® polymers (RSD = 0.0 - 1.0%), then by directly compressed Ethocel® Standard FP Premium polymers tablets (RSD = 0.3-1.0%) and finally the tablets having granular Ethocel® polymers prepared by direct compression method (0.3-2.9%). In general, the friability values were fairly comparable, with slightly lower values for the tablets having granular Ethocel® polymers as binders, especially those of higher viscosity grades; and slightly higher values for the directly compressed tablets with Ethocel® Standard FP Premium polymers. All the formulation had the friability value < 0.382 %.

During tablet preparation using the direct compression method it was revealed that the granular Ethocel® with lower viscosity grades allowed production of harder tablets than those of higher viscosity grades. In order to separate the hardness effect from constituent effect, tablets incorporating each Ethocel® grade were compressed, separately, to a hardness level in the range of 6 to 7kg by varying the compression force. With an increase in viscosity grade and the corresponding particle size, a decrease in compressibility was observed. Tablets with required hardness were achieved with each of the lower viscosity grade and fine particle size polymer using reduced pressure. The reason quoted is that the smaller particle size and fragmentation rate of Ethocel® with lower molecular weight (viscosity grade) are more effective than those with higher molecular weights, regarding the compressibility of tablets (Nystrem and Alderman, 1993). On the other hand the wet granulated tablets exhibited excellent compressibility characteristics in all the formulations studied, with slight differences positively deviated in favor of the tablets formulated with granular Ethocel® polymer, especially those at higher viscosity grades.

***In vitro* drug release studies:** The release profiles of from directly compressed granular Ethocel® matrices with different viscosity grades, at various D:P ratios are shown in Fig. 2. It can be observed that Ethocel® 7-cp demonstrated the slowest and Ethocel® 100-cp the fastest release rates among the formulations containing the granular Ethocel® polymers. This is because that tablets containing granular Ethocel® with lower viscosity grades were more compressible, providing harder tablets with lower porosity. On the other hand Ethocel® with higher viscosity grades granular polymer with larger particle size and thus higher porosity might not have produced a matrix with pores or openings small enough to trap the drug and retard its release rate. Moreover, the release profiles show that the influence of viscosity grade on drug release rates from the formulations containing granular Ethocel with intermediate viscosity grades is not quite noticeable. It is because that the Ethocel® is water-insoluble and no hydration of ethylcellulose occurred during dissolution test, consequently the polymer viscosity grade had little effect on the drug release rates. These results confirmed, partially, the findings of Shlieout *et al*. (1996) and Upadrashta *et al*. (1993) that ethylcellulose with lower viscosity grades produced slower release rates. However, these results contradict the statement of Shaikh *et al*. (1987) that higher the viscosity grade of ethylcellulose the slower the release of (water-soluble as well as sparingly soluble) drugs from the tablets.

While considering the effect of D:P ratios on the release rates of IBF, it could be observed that an increase in the amount of Ethocel® decreased the drug release rates. This might be attributed to the strength of the matrix because the matrix at higher concentration of Ethocel® should be, expectedly, stronger. This kind of matrix would cause a decrease in the size and an increase in the diffusional path length, which, in turn, will reduce water penetration through the micropores and drug diffusion, resulting in slower release rates. The effect of polymer content in the matrix containing the Ethocel® 20 cp polymer at D:P ratio of 10:2 during the extended dissolution period and that of Ethocel® 10 cp polymer at D:P ratio of 10:3 during the initial hours of the test, when compared with their respective D:P ratio of 10:1, on the drug release rate was not clear.

Release profiles from the Ethocel® matrices, as function of D:P ratio and viscosity grade of the polymer, were compared visually as well as by means of f_2 metric technique (Table 3). By the visual inspection of Fig. 2 (upper) there could be seen little differences between the cumulative percentage released at the end of 24hr from the matrices containing Ethocel® 7, 10, 20, and 45 cp at D:P ratio of 10:1. On the other hand the use of f_2-metric technique indicated that differences between the release profiles from the matrices with Ethocel® 10 cp, when compared with the reference (Ethocel® 7 cp) were, in fact, not so significant (f_2 = 53.25, >50), however, differences between the release profiles from the matrices containing Ethocel® 20 and 45 cp {f_2 = 49.95 and 39.87, respectively (<50)} when compared with the reference, were quite significant (Table 3). Similarly, at D:P ratios of 10:2 and 10:3 (Fig. 2, middle and lower), the computed f_2 values in all the cases were <50 (Table 3) indicating the significant differences among the dissolution performance of these formulations.

All these formulations in this investigation demonstrated a drastic decrease in the dissolution rates of the drug from the wet granulated tablets (Fig. 3), which could be attributed to the excellent compressibility of the granulations, producing harder tablets with lower porosity which might have stronger interparticle attractive/binding forces. In this way there will be a decrease in the water penetration rate through the micropores into the matrices, resulting in slower drug diffusion and consequently slower release rates of the drug from such tablets. Our results, in this respect, contradict those of Shlieout *et al*. (1996) where an increase in the dissolution rates of the drug with wet granulation occurred which was attributed to a probable increase in the erosion rates of the drug from ethyl cellulose matrices.

Ethocel® Standard Premium (granular) vs. Ethocel® Standard FP Premium polymers: Fig. 4 showed the comparative release profiles from the directly compressed tablets containing Ethocel® Standard 7, 10, 100 cp premium and 7, 10, 100 FP Premium polymers at different D:P ratios. f_2 values calculated by the f_2-metric technique are presented in Table 3, which determine the equivalence between the dissolution profiles and further clarify the well-defined differences (f_2 < 50 in all cases) in the drug release rates from the above mentioned formulations. It could be observed (Fig. 4) that Ethocel® Standard FP polymers extended the release rates of IBF more efficiently as compared to the conventional granular form of Ethocel®. The reason was still the exemplary small particle size of the Ethocel® Standard FP polymers. As seen in Fig. 4, granular Ethocel® Standard 7 cp released 89.7, 83.8 and 74.8% of IBF after 24 hr from the tablets at D:P ratios of 10:1, 10:2, and 10:3, respectively. On the other hand Ethocel® Standard 7 FP Premium with similar D:P ratios released, respectively, 73.5, 60.5 and 49.4 % after 24hr. The cumulative percentage of the drug released from Ethocel® Standard 10 cp and 10 FP Premium polymers at above D:P ratios were 92.5, 85.1, 74.0% and 67.2, 53.1, 42.5%, respectively. Similarly, Ethocel® Standard 100 cp and

Ethocel® Standard 100 FP Premium polymers released 97.8, 91.02, 88.7% and 92.6, 59.01, 36.8%, respectively, at the above mentioned D:P ratios. These results led us to the conclusion that polymer level and particle size, rather than viscosity grade, were the rate determining factors in controlling the release rates of IBF from the Ethocel® matrix tablets.

Fig. 5 showed that the comparative release profiles of IBF from directly compressed and wet granulated tablets containing Ethocel® Standard FP polymers with different viscosity grades at D:P ratio of 10 :3. Here again the wet granulation technique seemed to be dominant regarding the retardation in the release rates of IBF, due to the fore-mentioned reasons. These matrices demonstrated almost similar release profiles, irrespective of the polymer particle size and/or viscosity grade (with only slight positively deviated results in favor of Ethocel® Standard 10 FP at extended dissolution period), contrary to those obtained from the granular Ethocel® matrices through wet granulations. This could be attributed to the similar compressibility and other physical properties of the granulations achieved from the three grades of the Ethocel® Standard FP polymers.

From this research work concluded that both the conventional granular Ethocel® as well as Ethocel® Standard FP polymers have the potentials for a successfully prepared directly compressed CR tablet formulation of IBF. However, Ethocel® Standard FP polymers were found to be more efficient, promising, and suitable in this regards. Granular Ethocel® Standard polymers with lower viscosity grades were having greater compressibility than those of the higher viscosity grades. Polymer level and particle size, rather than viscosity grade, were found to be the determining factors in controlling the release rates of IBF from the matrix tablets. Moreover, both types of the polymers, at all D:P ratios and viscosity grades could control the release profiles of IBF from the matrices more efficiently, when prepared by wet granulation as compared to the direct compression method.

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