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Optimization of in situ forming intragastric oral formulations with different grades of PEGs

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ABSTRACT

The drug release profiles were optimized using different grades of polyethylene glycols (PEGs). Phase diagrams of ternary mixtures of ethylcellulose, PEG and TEC were obtained and used for optimization of drug release. The phase diagrams showed that addition of higher molecular weight of PEGs increased the phase separation and caused precipitation of ethylcellulose from the ternary mixtures. The effect of different grades and concentrations of PEGs in novel oral intragastric controlled release gel formulations were also investigated. In conclusion, the in situ forming oral controlled release formulations were successfully developed and the formulations were able to control the release of hydrochlorothiazide up to 24 hours.

KEYWORDS: Ethylcellulose, PEG, TEC, Phase diagrams, Ternary mixtures, Hydrochlorothiazide

RESUMEN

Los perfiles de liberación farmacológica se optimizaron mediante diferentes grados de glicoles de polietileno (PEGs). Se obtuvieron diagramas de fase de mezclas ternarias de etilcelulosa, PEG y TEC, que se usaron para optimizar la liberación farmacológica. Los diagramas de fase mostraron que la adicción de PEGs de mayor peso molecular incrementaba la separación de fases y causaba precipitación de etilcelulosa de las mezclas ternarias. Se investigó también el efecto de distintos grados y concentraciones de PEGs en nuevas formulaciones de geles orales de liberación controlada intragástrica. En conclusión, las formulaciones orales de liberación controlada in situ se desarrollaron con éxito y fueron capaces de controlar la liberación de hidroclorotiazida hasta 24 horas.

PALABRAS CLAVE: Etilcelulosa, PEG, TEC, Diagramas de fase, Mezclas ternarias, Hidroclorotiazida

INTRODUCCIÓN

Polyethylene glycols (PEGs) have been widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. PEGs are available in different molecular grades, and the physicochemical properties of these grades are quite different from one another (table1). High molecular weight PEGs (m.w. > 4000) have been used as binders and lubricants for soluble tablets, whereas, low molecular grade PEGs have been used for injectable, ophthalmic and nasal preparations. In addition, they have been used as plasticizers for polymers utilized for film coating and microencapsulation.[1] PEGs and their derivatives have also been used as wetting and channeling agents to increase oral bioavailability of poorly soluble drugs such as rofecoxib,[2] ketoconazole,[1] glibenclamide,[3] prednisolone,[4] and many more.[5] Leonardi et al., have studied the stability of prednisolone solid dispersion in PEG 6000 using scanning electron microcopy (SEM), infrared (IR) spectroscopy, and X-ray powder diffraction techniques.[6] The stability study showed that the drug was stable, without any interaction between the prednisolone and PEG 6000 at different stability conditions for one year. Similar results were reported for rofecoxib-PEG 4000 solid dispersions.[2]

In this study, unique in situ forming intragastric oral formulations (ISFIOFs) were prepared with a blend of a hydrophobic polymer, Ethocel and solvent (TEC). These formulations can be utilized as potential oral controlled drug delivery systems. Some of the advantages of the ISFIOFs are that they are easy to manufacture and scale up because of the less processing steps. In addition, they can also be developed as tamper-proof dosage forms of controlled substances, and drug release profiles can be easily modulated from these formulations by changing the formulation factors. However, the ability of these formulations to withstand mechanical stress is an important aspect of controlled release ISFIOFs in order to prevent dose dumping. Furthermore, the formulation should be able to release the entire drug during a specified time frame. In general, the mechanical strength of ISFIOFs can be increased by increasing the solid content such as, polymer concentration in the formulation. However, the drug release kinetics is strongly affected by changes in the polymer concentration. Therefore, to obtain a formulation with adequate mechanical strength and the one that provides optimum drug release is challenging. To overcome these challenges, different grades of PEGs were used as channeling and bulking agents for the ISFIOF formulations in this study. Upon addition of PEGs, the ISFIOFs are converted to ternary mixtures. For any stable ternary phase mixture, an adequate balance of hydrophilic and lipophilic molecules is essential. The relative amounts of three components in a system can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the weight or volume fractions of the different components on the phase behavior of the system.[7] In a typical phase diagram, the three components comprising the system are each found at an apex of a triangle, where their corresponding weight or volume fraction is 100%. At any point away from the apex, the weight or volume fraction of a specific component is reduced, while the weight or volume fraction of one or both of the two other components is increased. Each point within the triangle represents a possible composition of a mixture of the three components. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant

Tabla1. Physical properties of different grades of PEGs.[8]

PEG grades	Supplied form	AMW (range)	T (°C)	S-20°C (%w/w)	Viscosity* (cSt)	LD (g/mL)
200	Liquid	190 to 210	-	Complete	4.3	1.0921
300	Liquid	285 to 315	-15 to -8	Complete	5.8	1.0927
400	Liquid	380 to 420	4 to 8	Complete	7.3	1.0931
600	Liquid	570 to 630	15 to 25	Complete	10.8	1.0931
1000	Fused solid	950 to 1050	35 to 40	80	17.2	1.0927
1450	Flake	1305 to 1595	42 to 46	72	26.5	1.0919
3350	Granular powder	3015 to 3685	53 to 57	67	90.8	1.0926
4000	Granular powder	3600 to 4400	53 to 59	66	140.4	1.0926
4600	Granular	4140 to 5060	54 to 60	65	183.9	1.0926
6000	Granular	5400 to 6600	55 to 61	64	320	-
8000	Granular powder	7000 to 9000	55 to 62	63	821.7	1.0852

AMW: Average Molecular Weight; T: Melting or Freezing temperature; S-20: Solubility in water at 20°C; LD: Liquid density at 60°C
* Viscosity at 100°C;

temperature and pressure. The phase diagram can be used to identify regions in which the ternary phase is stable or uniform. Therefore, the objective of this study was to use the phase diagrams to identify the amounts of different grades of PEGs, which can be used to prepare novel ISFIOFs, with adequate mechanical strength and optimum drug release profiles.

MATERIALS AND METHODS

Materials

Ethocel 10 FP and polyethylene glycols PEG 400, PEG 1450, PEG 3350, PEG 4600 and PEG 6000 were obtained from Astron Chemical Ltd, Gujarat. Triethyl citrate (TEC) was obtained from Morflex Inc., Greensboro, NC. Hydrochlorothiazide (Torrent Research Center, Ahmedabad) was used as a model drug.

Methods

1. Phase diagrams

Phase diagrams were constructed with different concentrations of different grades of polyethylene glycols (PEGs), namely, PEG 400, 1450, 3350, 4600 and 6000, Ethocel 10 FP, and triethyl citrate (TEC). Blank gel formulations were prepared from different concentrations of Ethocel 10 FP and TEC at 70oC. PEG was added to the resultant blank gel. The concentrations of the PEGs used in the gel formulations were 5, 10, 15, and 20% w/w, whereas the concentrations of Ethocel 10 FP were 5, 10, 15, 20, 25% w/w. The ternary blends, which yielded clear gels and the ones in which Ethocel precipitated were plotted as phase diagrams. The ratios of all the three ingredients, which formed a clear and uniform ternary blend at 70oC were identified from the phase diagrams, and controlled release drug loaded gel formulations were prepared using these ratios.

2. Formulation optimizations

In situ forming novel oral controlled release gel formulations (ISFIOFs) were prepared with different concentrations of Ethocel 10 FP, triethyl citrate (TEC) and different grades of polyethylene glycols, namely, PEG 400, 1450, and 3350. A total of 10 different formulations were prepared as listed in Table 2. The formulations were prepared as follows: Appropriate amounts of polymer (Ethocel 10 FP) and solvent (TEC) were mixed in a glass beaker and heated up to 70ºC with constant stirring. The polymers dissolved in the solvents and formed blank gels. Appropriate amounts of PEGs were then added to the resulting mixtures with continuous stirring. The PEGs melted in the blank gels and formed a homogeneous ternary mixture. The grades and concentrations of the PEGs were selected from the phase diagrams such that the resulting ternary system consisting of Ethocel 10 FP, PEG and TEC formed a clear blank gel. An appropriate quantity of hydrochlorothiazide was then added to the blank gel with continuous stirring. The resultant drug-loaded gel formulation was poured into a heated glass syringe, which was used as a capsule-filling device. Pre-weighed hard gelatin capsules, size 00, were filled with the gel formulation, capped and stored at room temperature until further use.

3. Determination of release profiles of hydrochlorothiazide

Drug release from three capsules of each drug-loaded gel formulation was evaluated using the USP Apparatus II at 50 rpm. Phosphate buffer, pH 6.8 (900 ml) at 37 ± 0.5°C was used as the dissolution medium. Samples were taken at 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours. Hydrochlorothiazide concentrations in the withdrawn samples were determined using a double beam UV-Spectrophotometer (Shimadzu, Model 1800) at 272 nm. The cumulative percentages of hydrochlorothiazide in the collected dissolution samples

Table 2. Composition of formulations prepared with different grades of PEGs.

Batch number	PEG grade	Composition of blank gels			Drug loading (% w/w)
		PEG (%)	Ethocel® 10 FP (%)	TEC (%)	
R1	3350	00	15	85	10
R2	3350	05	15	80	10
R3	3350	10	15	75	10
R4	3350	15	10	75	10
R5	3350	15	10	75	15
R6	3350	15	10	75	20
R7	1450	15	10	75	15
R8	400	10	15	75	15
R9	400	15	10	75	15
R10	400	25	10	65	15

were calculated from the cumulative amount of drug released at specific time intervals and plotted.

RESULTS AND DISCUSSION

1. Phase diagrams

Phase diagrams showed that addition of higher molecular weights of PEGs increased the phase separation and caused precipitation of ethylcellulose from the ternary mixtures of ethylcellulose, PEG and TEC (figures 1, 2, 3, 4 and 5). Gel formulations prepared from blends of ethylcellulose, TEC and PEG 400 gave a broader working range compared to those prepared from blends of ethylcellulose, TEC and PEG 6000. For example, up to 30% PEG 400 could be incorporated into the gel formulations prepared with 10% Ethocel 10 FP and TEC without precipitation, whereas up to 15% PEG 1450, 15% PEG 3350, 10% PEG 4600 or 5% PEG 6000 could be incorporated into the gel formulations prepared with 10% Ethocel 10 FP and TEC without precipitation. Based on the phase separation studies, PEG 400, 1450 and 3350 were selected for further studies. PEG 4600 and 6000 were not used for further studies due to their narrow working ranges.

2. Effect of different concentrations of PEG 3350

Since PEG 3350 is solid at room temperature and can be used as a bulking agent, initial gel formulations were prepared with PEG 3350. The release profiles of hydrochlorothiazide from the gel formulations prepared with 15% Ethocel 10 FP, different concentrations of PEG 3350 and TEC are shown in Figure 6. It is evident from the figure that as the PEG 3350 concentration increased from 0 to 10% in the gel formulation prepared with 15% Ethocel 10 FP, the drug release decreased from 72% to 50%, respectively, at 24 hours. This is because, increasing the PEG content from 0 to 10% increased the solid content of the gel formulation, thus resulting in faster precipitation of solid mass in the dissolution medium. Hence, burst release and overall drug release from the gel formulation prepared with PEG 3350 was less than those prepared without PEG 3350.

Drug release form a rigid solid mass can be increased by creating pores and channels. Therefore, in order to increase the drug release from gel formulation prepared with blends of 15% Ethocel 10 FP, 10% PEG 3350 and TEC, the Ethocel 10 FP concentration in the abovementioned gel formulation was decreased from 15 to 10%, and the PEG 3350 concentration was correspondingly increased from 10 to 15%. These modifications of the gel formulations led to an increase in drug release from 50% (for gel formulation prepared with 15% Ethocel 10 FP, 10% PEG 3350 and TEC) to 84% (for gel formulation prepared with 10% Ethocel 10 FP, 15% PEG 3350 and TEC) at 24 hours (Figure 6).

Figure 1. Phase diagram of a tertiary system of Ethocel® 10 FP, TEC and PEG 400.

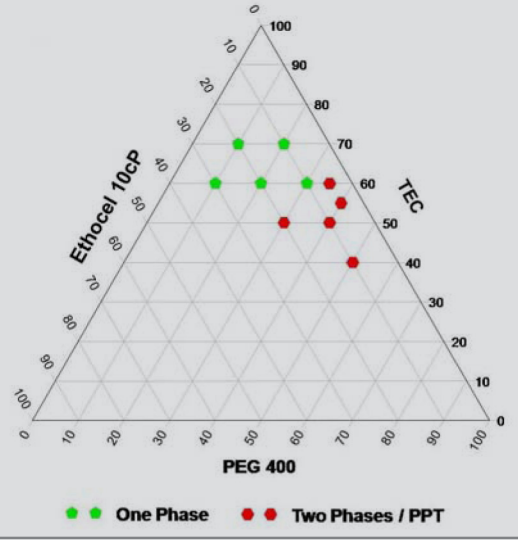


Figure 2. Phase diagram of a tertiary system of Ethocel® 10 FP, TEC and PEG 1450.

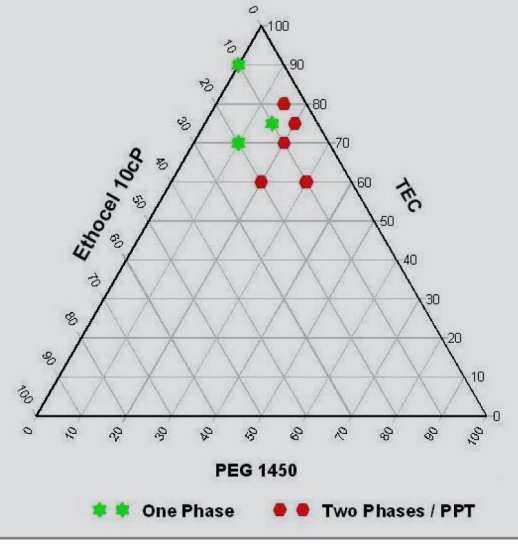


Figure 3. Phase diagram of a tertiary system of Ethocel® 10 FP, TEC and PEG 3350.

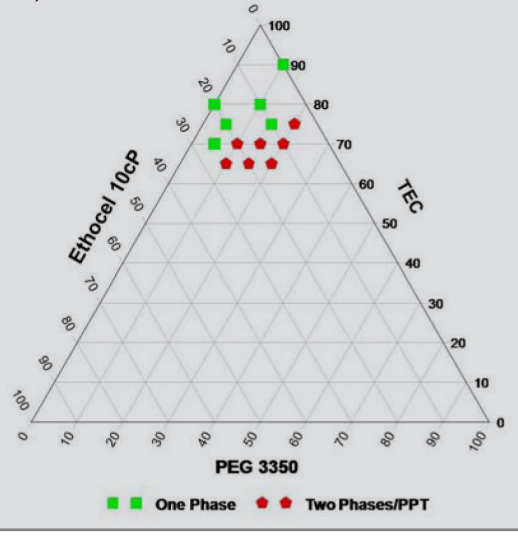


Figure 4. Phase diagram of a tertiary system of Ethocel® 10 FP, TEC and PEG 4600.

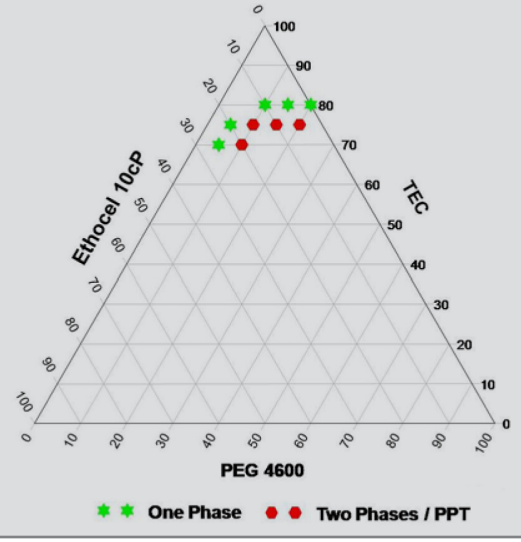
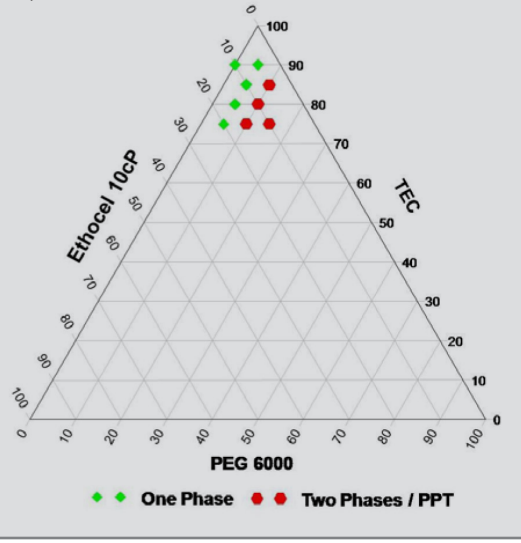


Figure 5. Phase diagram of a tertiary system of Ethocel® 10 FP, TEC and PEG 6000.



3. Effect of different grades of PEGs

Figure 7 shows drug release from gel formulations prepared with blends of 10% Ethocel 10 FP, 15% of two different grades of PEGs (PEG 1450 and PEG 3350) and 75% TEC. It is evident from the figure that a higher burst release (14% at 1 hours) was observed from the gel formulation prepared with the low molecular weight PEG 1450 than that prepared with the high molecular weight PEG 3350 (6% at 1 hours). This was because the low molecular weight PEG 1450 leached out faster than PEG 3350 from the gel formulations.

However, after the first two hours, drug release from the gel formulation prepared with PEG 3350 was slower than that from gel formulation prepared with PEG 1450. This was because faster leaching out of the low molecular weight PEG 1450 from the gel formulation resulted in quicker precipitation of the Ethocel 10 FP on the exterior of the gel formulation and thus formation of a rigid shell around the gel. This rigid shell of precipitated Ethocel 10 FP retarded the penetration of the dissolution fluid into the solid mass thus resulting in slower drug release from gel formulation prepared with PEG 1450 (65% in 24 hours) compared to that prepared with PEG 3350 (95% in 24 hours). Gel formulation prepared with PEG 400 was dissipating in the dissolution medium and hence showed an erratic drug release profile (data not shown).

Figure 6. Effect of PEG 3350 on drug release from gel formulations prepared with different concentrations of Ethocel® 10 FP and PEG 3350.

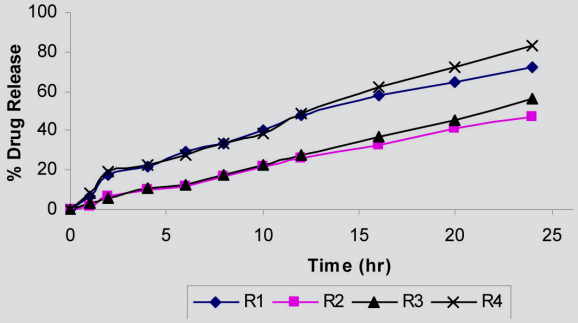
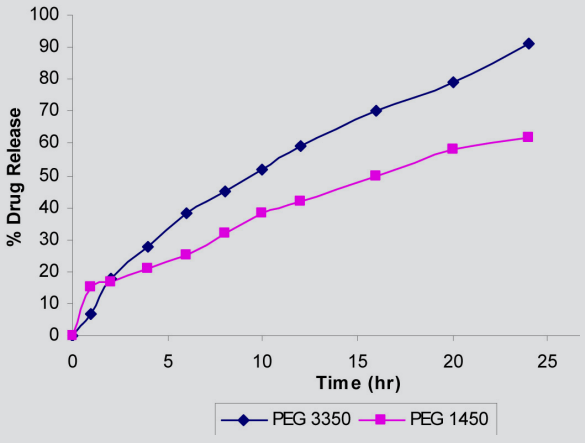


Figure 7. Effect of different grades of PEGs on drug release from gel formulations prepared with 10% Ethocel® 10 FP, 15% PEG 3350 and 75% TEC with 15% drug loading.



4. Effect of different drug loading

As the drug loading in the gel formulation prepared with 10% Ethocel 10 FP, 15% PEG 3350 and 75% TEC was increased from 10% to 20%, the drug release rate was also increased (Figure 8). For example, 84% of the drug was released in 24 hours from gel formulations prepared with 10% drug loading, whereas, 95% of the drug was

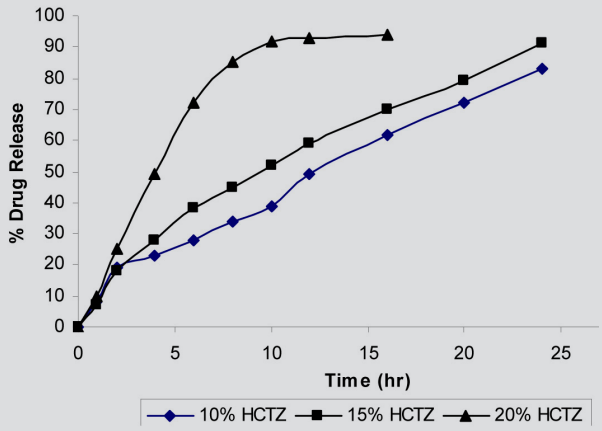
released from the gel formulation prepared with 15% drug loading. However, 93% of drug was released in 10 hours from gel formulation prepared with 20% drug loading. The variation between drug release profiles of individual capsules was the highest from gel formulations prepared with 20% drug loading. However, the variation in all the drug release profiles were seen after 50% of the total amount of drug was released. A reproducibility study was performed on eight different capsules randomly selected from three different batches of optimized gel formulation (R5) in order to confirm the variability in the drug release profiles.

Hence, this study showed that the rheology of the gel formulation prepared with 10% Ethocel 10 FP changed quickly. At the same time, the hydrophilic components such as the water-soluble drug, hydrochlorothiazide and the bulking agent, PEG 3350, in the gel formulation, also released continuously from the gel formulation. As a result, the total solid content of the gel formulation decreased. Both these phenomena, i.e. rheological changes, and the changes in the total solid contents altered the gel structure into a solid mass, initially at a slower rate, albeit at a controlled manner; while in the later stages, at a faster rate, but in an uncontrolled manner. Therefore, the final 30 to 40% of the drug was released in an erratic and an uncontrolled manner from the remaining solid mass. The solid mass remaining at the end of the dissolution study had sea-coral like structures with irregular pores and channels. The drug release profile also showed that the standard deviations of the drug release profiles increased after 50% of the drug was released from the gel formulation.

CONCLUSION

Phase diagrams of ternary mixtures of ethylcellulose, PEG and TEC were constructed and used for optimization of drug release from unique ISFIOF. Phase diagrams showed that addition of higher molecular weight PEGs increased the phase separation and caused precipitation of ethylcellulose from the ternary mixtures. Gel formulations prepared from blends of ethylcellulose, TEC and PEG 400 gave a broader working range compared to those prepared with blends of ethylcellulose, TEC and PEG 6000. Drug release from novel oral controlled release gel formulations were affected by different grades of PEGs. Drug release studies showed that low molecular weight PEG leached out faster from the gel formulation, thus giving higher burst release than that prepared with a high molecular weight PEG. Drug release from the optimized dosage form of ISFIOF, which was prepared with 10% Ethocel 10 FP, 15% PEG 3350, 75% TEC with 15% drug loading.

Figure 8. Effect of different drug loadings on drug release from gel formulations prepared with 10% Ethocel® 10 FP, 15% PEG 3350 and 75% TEC



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