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Invited Article

Multiple Unit Asymmetric Membrane Capsule: A Means for Delivery of Highly Water Soluble Drug

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ABSTRACT
A multiple unit, non-disintegrating asymmetric polymeric capsular system was used to deliver highly water-soluble drug in a controlled manner. A highly water-soluble drug, metformin hydrochloride (MHCl), was selected as a model drug to demonstrate how the controlled release could be generated *in vitro* by changes in the core as well as the coating formulation. Formation of asymmetric capsule wall membrane involved wet phase inversion process, in which the asymmetric membrane (AM) was precipitated on glass mold pins by dipping the mold pins into a coating solution containing the good and bad solvents for the polymer followed by quenching in an aqueous quench bath. The study optimized by 2^3 factorial design evaluates the influence of coating formulation namely concentration of ethylcellulose and pore former (glycerol) and core component namely controlled release potassium chloride crystals. Scanning Electron Microscopy (SEM) showed the presence of outer dense non porous region and inner, thick, porous region for the prepared AM. Statistical test were applied at $P > 0.05$ on all the formulations undergoing *in vitro* release studies. Results showed the solubility of MHCl to have been modulated (reduced) over an extended period of time with pH independent, and osmotic pressure dependant drug release. The release kinetics was found to be zero order.

Keywords: Solubility modulation, asymmetric membrane capsule, multiple unit, factorial design, zero order.

INTRODUCTION

In recent years, development of novel drug delivery systems (NDDS) has become a part of scientific research. Among the various NDDS, osmotic drug delivery systems hold a major share in the pre-oral controlled release (CR) systems because of the obvious advantages of being independent from the influence of pH, presence of food and other physiological factors. Various types of osmotic pumps have been reviewed by Santus and Baker. [1] The elementary osmotic pump (EOP) which was comparably simple to manufacture and was able to release drug at an approximate zero order rate, was first introduced by Theeuwes in 1970s. [2] EOPs, however were suitable for the delivery of water soluble drug. To overcome the limitation of EOP, a push pull osmotic tablet was developed, but these also had two disadvantages 1) The tablet core was prepared by compressing two kinds of compartments together, a complex technology as compared with that of EOP and 2) After coating, a complicated laser drilling technology was employed to drill an orifice next to the drug compartment. [3] Osmotic tablets with an asymmetric membrane coating, which can achieve high water fluxes, have been described. [4] The asymmetric membrane capsule (AMC) described is an example of a single core osmotic delivery system consisting of a drug containing core surrounded by an asymmetric membrane. The use of AMC primarily has been for delivery of poorly water soluble drugs. [5-6] The kinetics of osmotic drug release is directly related to the solubility of the drug within the formulation. Highly water-soluble drugs will demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Therefore, it becomes imperative to control the process of the drug's ability to form a solution.

Therefore, the aims of this work were 1) To develop controlled release solubility modifier and asymmetric membrane capsule to deliver highly water-soluble drug such as promethazine hydrochloride (PHCl) in a controlled manner and 2) To evaluate the influence of variables based on 2^3 factorial design apart from evaluating the effect agitational intensity and different osmotic pressure on the drug release from the prepared AMCs.

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MATERIALS AND METHODS

Materials

PHCl was gift sample from Siemen Lab, Gurgaon, India. Sodium di hydrogen phosphate and di sodium hydrogen phosphate (both analytical reagent grade) were purchased from s. d. fine chemicals, Mumbai, India. Ethyl cellulose (EC, 50cps), glycerol, acetone, and ethanol were obtained from Qualigens Pvt. Ltd., Mumbai, India. Sodium chloride (NaCl) from Merck India, New Delhi, was purchased from C.N. Chemicals, Uttar Pradesh, India, was used as supplied. Solvents of reagent grade and double distilled water were used in all experiments.

Equilibrium Solubility Studies

Kinetics of osmotic drug release is directly related to the solubility of the drug inside the formulation. Therefore, to access the solubility of the drug in various mediums saturated solutions of the drug were prepared in 0.1 N HCl, phosphate buffer pH 7.4, and doubled distilled water and 0.00 M, 0. 50 M, 1.00 M, 1.50 M and 1.75 M NaCl solution in a closed container and maintained at 37°C. The containers were shaken for 72 h followed by filtration and spectrophotometric analysis at 249 nm. The condition of 37°C was also maintained during filtration until the time of analysis by specially designed temperature controlling boxes to prevent any precipitation of drug due to sudden change in temperature.

Solubility Modulation by Formation of Controlled Release Sodium Chloride Crystals (CR NaCl)

Since the solubility of PHCl was found to be very high (>500 mg/ml), a first-order release kinetics of PHCl rather than the desired zero-order was anticipated. Zero order release would only be possible if the solubility could be decreased substantially. Consequently, in order to make a control release formulation of this drug, solubility modulation approach was used by preparing CR NaCl. The CR NaCl, to be incorporated into the cores to achieve the required molar environment were prepared from sifted (# 16) NaCl crystals that were coated with a 1% w/w, 3%w/w and 5% w/w solution of EC, and 8% w/v glycerol in acetone (20% v/v) and ethanol (35% v/v) using fabricated fluidized bed drier (FBD lab Model No. 1)

Characterization of CR NaCl

Characterization of CR sodium chloride was done with regard to micromeritic studies namely angle of repose and Hausner ratio, and their release profile, in which 500 mg of uncoated NaCl crystals and coated CR NaCl crystals were incorporated into the prepared asymmetric membrane capsules (AMC) and designated as AMCS1, AMCS2, AMCS3 and AMCS4 respectively. The amount of NaCl from all the formulations was assayed as per the standard assay procedure for NaCl given in I.P

Preparation of Asymmetric Membrane Capsules (AMC)

AMCs were prepared by using the wet phase inversion process as previously reported. [9] However, the coating composition of the coating solution varied. The glass mold pins were dipped in a coating solution of 10% w/v and 15% w/v of EC and varying amounts of glycerol (10 %w/v and 15 % w/v) dissolved in acetone (50 % v/v) and ethanol (30 % v/v for 10% w/v glycerol and 25 % v/v for 15% w/v glycerol), and air dried for 15 seconds. After this, the pins were immersed in an aqueous quenching solution (10% w/v of glycerol) for 10 minutes. Immersion of EC coated glass mold pins in a quench bath helped in generation of asymmetric membranes. Asymmetric membranes in shape of the body and cap of conventional capsules were then stripped after removal from the quench bath and dried at ambient temperature for at least 8 h. The body and the cap were then trimmed to fit inside each other for formation of the AMC. Drug loading of 200 mg, based on Equation 4, after passing through 100 mesh sieve, and having particle size 120-130 µm, was mixed with CR NaCl (360 mg and 400 mg) in a polythene bag, and the AMCs were filled manually. CR NaCl was used as a solubility modifier and an osmogen as PHCl was found to be osmotically inactive. [7] The filled AMCs were sealed with an 10 % v/v ethanolic solution of EC. The physical characterization of AMC with a conventional hard gelatin capsule (HGC) is given in Table 1. The composition of all the AMCs formed, along with the extra design checkpoint AMC (AMC 9) is represented in Table 2.

Scanning Electron Microscopy (SEM)

Asymmetric membrane (10% w/v and 15 % w/v glycerol concentration) were examined for their porous morphology before and after dissolution by SEM (Jeol 6000, Tokyo, Japan). Membranes were air dried for 12 h and stored between sheets of wax paper in a dissector before examination. The AM samples were sputter coated for 5-10 min with gold by using fine coat in sputter (Jeol 6100) and examined under SEM.

Differential Scanning Calorimetry (DSC)

The DSC profiles of pure and physical mixtures of PHCl were recorded on Pyris Diamond DSC-4 (PerkinElmer, Wellesley, MA). Thermal behaviors were studied under normal conditions with perforated and sealed quartz pans and with a nitrogen gas flow of 400 ml/min. The samples (11.36 mg for pure PHCl, 10.84mg for PHCl and CR NaCl, and 11.04 mg for PHCl, CR NaCl, and ethylcellulose) were heated at 5°C/min over a temperature range of 23 -300°C, 24-300°C and 18-300°C respectively. The reference sample used in all the three determinations was alumina with a weight of 10.5 mg. Peak temperatures and enthalpies were calculated as a mean of three measurements.

In Vitro Drug Release Study

In vitro drug release study was performed in 0.1N HCl for 2 h and rest of the period in pH 7.4 phosphate buffer using U.S.P. Apparatus II. An appropriate volume of sample was withdrawn at predetermined time intervals and assayed by a validated UV method for PHCl (wavelength 249 nm). The same volume of fresh medium was replaced to maintain constant volume for dissolution.

Optimization Studies

The selection of the optimized formulation was done using a 2^3 factorial design. Three factors namely concentration of ethylcellulose (10 % w/v and 15 % w/v), concentration of glycerol (5 % v/v and 10 % v/v) and concentration of controlled release osmotic agent (1.5 M and 1.75 M) were selected. The response parameter was chosen as $t_{50\%}$. The best formulation (optimized formulation) was selected based on the degree of correlation and similarity value (f_2) between the observed and predicted (extra design check point batch) $t_{50\%}$.The release profiles up to $t_{50\%}$ of PHCl from all formulations in the dissolution medium was statistically compared with help of Minitab statistical software (Minitab®, Graphpad, CA, U.S.A) with release rate profiles of the theoretical formulation (extra design checkpoint batch), which was obtained by using the polynomial equation. The statistical significance was tested at $P > 0.05$. The best formulation among the nonsignificant pairs of formulations was chosen after pair wise comparison using similarity factor (f_2) (PCP Disso Version 2.08 Software, Pune, India), and the formulation in the factorial design batch with the highest value of f_2 was selected as the best formulation.

Effect of Agitational Intensity

The effect of different agitational speeds on the drug release was studied. Release studies were carried out at three different speeds namely 50,100,150 rpm using U.S.P. Apparatus I, at 37°C ± 0.5°C and their effects on drug release profile were studied by analyzing the amount of drug release from the formulation at predetermined intervals at 249nm.

Table 1: Physical characterization of AMC as compared to conventional gelatin capsule (HGC)

Type	Appearance	Size				
		Cap (mm)		Body (mm)		Sealed(mm)
		Length	Diameter	Length	Diameter	
HGC	**Transparent**	9.02±0.12	6.12±0.12	16.08±0.12	5.09±0.02	19.08±0.09
AMC	**opaque**	9.02±0.14	6.13±0.14	16.04±0.17	5.14±0.17	18.99±0.17

Table 2 Composition of promethazine hydrochloride formulations

Variables	AMC 1	AMC 2	AMC 3	AMC 4	AMC 5	AMC 6	AMC 7	AMC 8
Promethazine hydrochloride (mg)	50	50	50	50	50	50	50	50
CR NaCl (mg)	360	360	400	400	360	360	400	400
EC (% w/v)	10	15	10	15	10	15	10	15
Glycerol (% v/v)	10	10	10	10	15	15	15	15
Acetone (% v/v)	50	50	50	50	50	50	50	50
Ethanol (95% v/v)	30	25	30	25	25	20	25	20
Water(mL) q.s	100	100	100	100	100	100	100	100

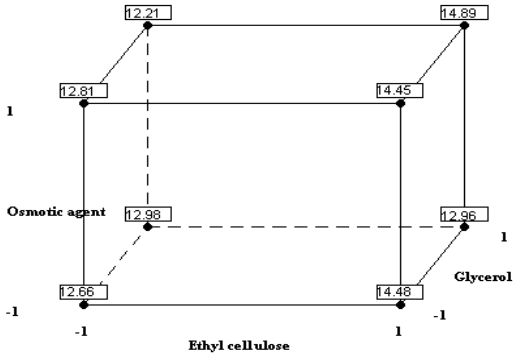


Fig. 1: Optimization studies using 2^3 factorial design with $t_{50\%}$ marked at indices

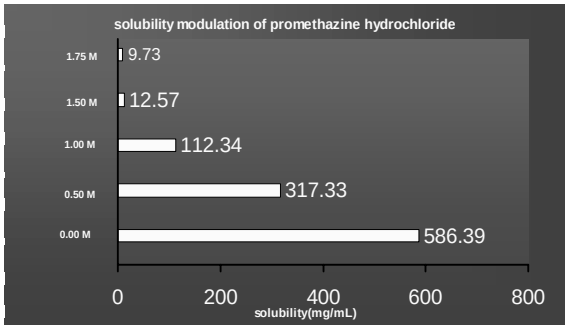


Fig. 2: Solubility modulation of promethazine hydrochloride using different molar concentrations of sodium chloride.

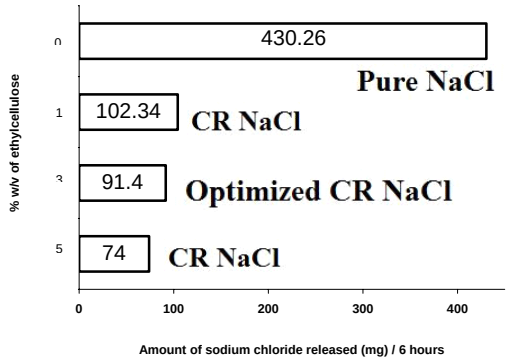


Figure 3. Comparative release profile of CR NaCl from different percentage of ethylcellulose coating

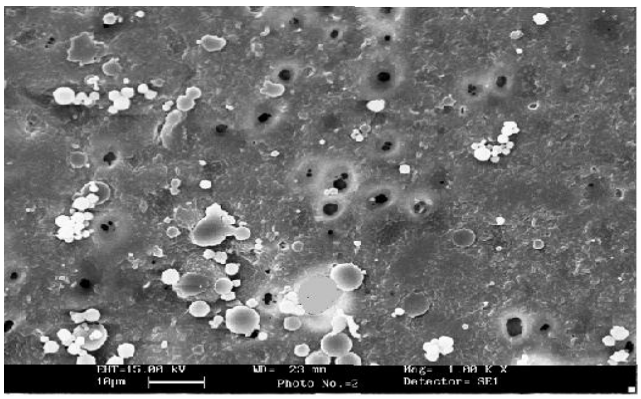


Fig. 4a: SEM photographs of asymmetric membrane depicting outer dense region with few pores

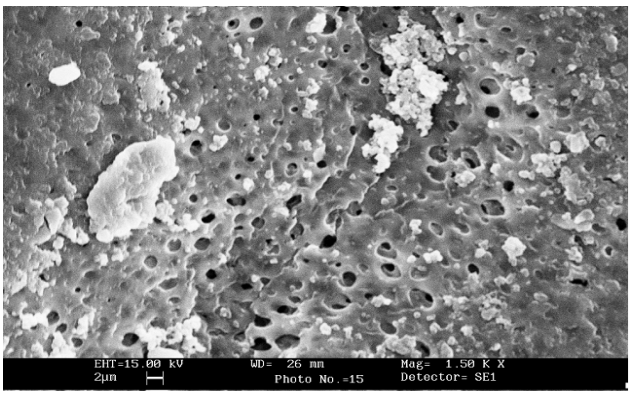


Fig. 4b: SEM photographs of asymmetric membrane depicting inner porous region.

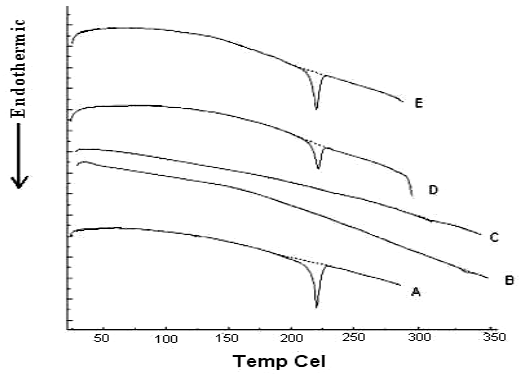


Fig. 5: DSC profile of promethazine Hydrochloride along with its mixtures

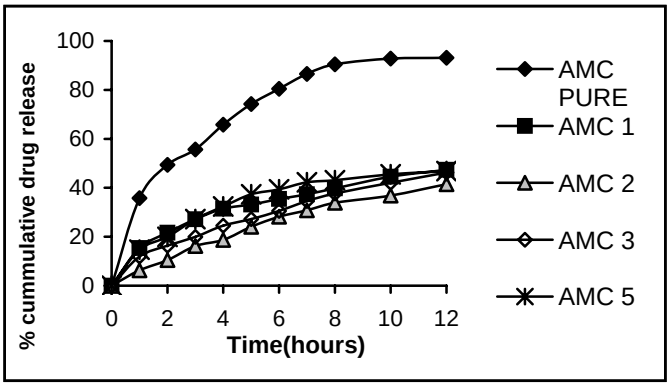


Fig. 6: Comparative release profile of group1 formulations

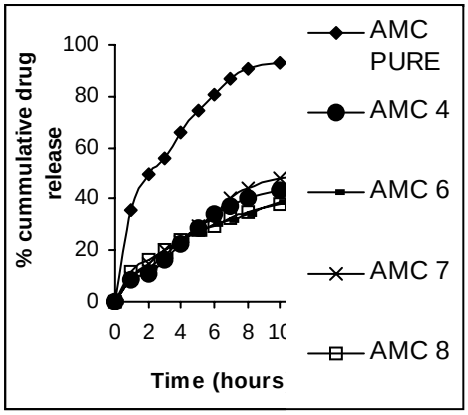


Fig. 7: Comparative release profile of group 2 formulations

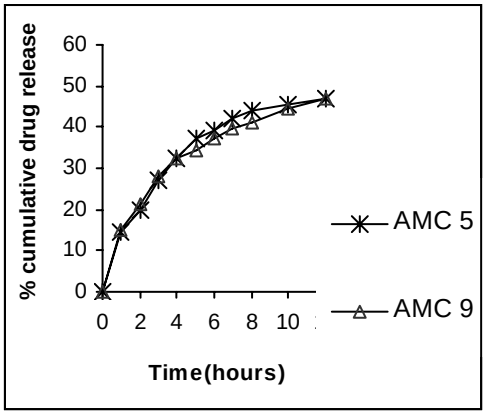


Fig. 8: Comparative release profile of AMC 5 and AMC 9

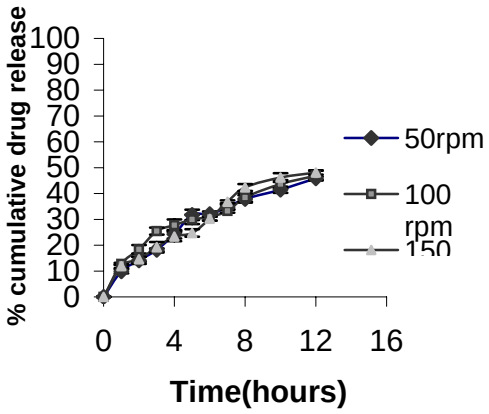


Fig. 9: Effect of agitational intensity on *in vitro* drug release of promethazine hydrochloride

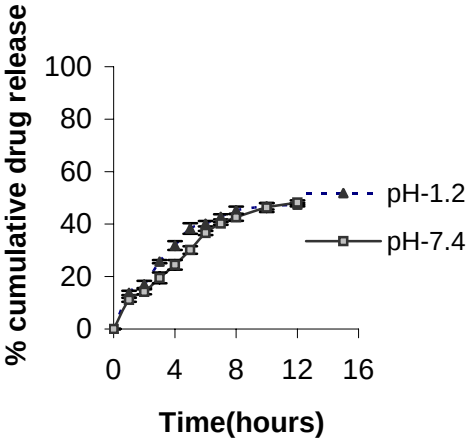
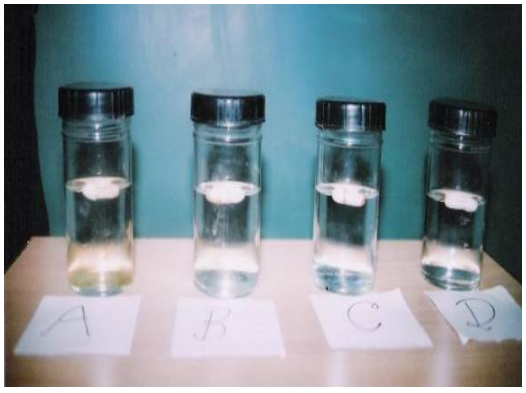
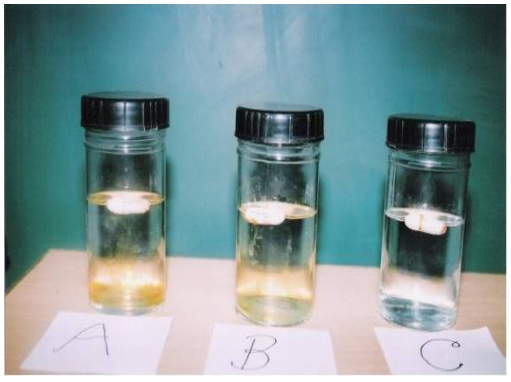


Fig. 10: Effect of varying pH on *in vitro* drug release of promethazine hydrochloride

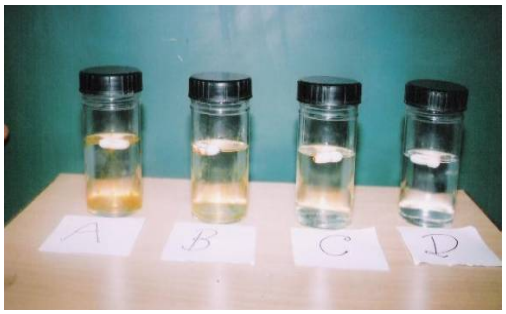


(*Plate 1*)



(*Plate 2*)

(*Plate 3*)



(*Plate 4*)

Fig. 11: Observed effects of osmotic pressure at different time on drug release (*Plate 1*) at 0 minutes, (*Plate 2*) after 5 minutes , (*Plate 3*) after 30 minutes, (*Plate 4*) after 1hour 30 minutes. Where A= AMC-A,50 mg $FeCl_3$ in distill water, B= AMC-B, 50 mg $FeCl_3$ + 90 mg NaCl in distill water , C= AMC-C,50 mg $FeCl_3$ + 90 mg NaCl in hypotonic solution and D= AMC-D, 50 mg $FeCl_3$ + 90 mg NaCl in hypertonic solution

Effect of pH of Dissolution Medium

The effect of varying pH on the drug release profile was measured using two different medium 0.1N HCl, and phosphate buffer pH 7.4. Drug release studies were carried out using U.S.P. Apparatus I, at 37°C ± 0.5°C for both the medium, and release profiles statistically compared using one-way ANOVA.

Effect of Common Ion and Osmotic Pressure on Drug Release

Osmotic pressure and common ion effect of the osmotic agent inside the formulation plays an important role in deciding the release of drug from the asymmetric membrane capsules. In order to demonstrate the above said, four different systems were selected (Fig. 1). For this experiment 50 mg $FeCl_3$ (a freely water soluble dye) was selected as a color producing dye whose release from the asymmetric membrane capsule was dependent on the molar environment created by NaCl inside the capsule. $FeCl_3$ (50 mg) without NaCl inside and outside the capsule (AMC-A) represented no tonicity condition. $FeCl_3$ (50 mg) with NaCl (500 mg) inside and 0 mg outside the formulation (AMC-B) also represented no tonic condition but was formulated to demonstrate the common ion effect. $FeCl_3$ (50 mg) and NaCl (500 mg) inside and 250 mg outside the formulation (AMC-C) represented the hypotonic condition. $FeCl_3$ (50 mg) and NaCl (500 mg) inside and 750 mg outside the formulation (AMC-D) represented hypertonic condition. Both AMC-C and AMC-D were formulated to demonstrate the effect of osmotic pressure on drug release. The release of $FeCl_3$ from all the systems were evaluated and interpreted.

Kinetics of Release

In general, the release of drug from an osmotic system depends on many factors such as osmotic pressure, pore size, and coating thickness. The zero-order rate describes systems where drug release is independent of its concentration and is generally seen for poorly water-soluble drug in matrix, transdermals, etc. [8] The first-order describes systems in which the release is dependent on its concentration (generally seen for water-soluble drugs in porous matrix). [9] The Higuchi model describes the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion. [10] The Hixson-Crowell cube root law describes the release of drug from systems where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in the case of systems that dissolute or erodes over time. [11]

RESULTS AND DISCUSSION

Equilibrium Solubility and Solubility Modulation Studies

The solubility of PHCl (37°C ± 5°C) in water was 586.39 mg/ml. The high solubility of PHCl was successfully reduced using different molar solution of NaCl. The theoretically expected zero-order release characteristics that would accompany the various NaCl modulated (reduced) PHCl solubilities were calculated. Concentration of NaCl maintained at 1.50 M in all the mediums studied showed reduced PHCl solubility (~ 12 mg/mL). Therefore, this molar concentration of NaCl was selected along with a higher molar concentration of NaCl (2.00 M) as the two levels after the optimization for concentrations of CR NaCl crystals to be used in the factorial design, and the results of *in vitro* release studies ($t_{50\%}$) was used as the response in the factorial design (Fig. 1).

The osmotically controlled drug release over a period of 24 h for a highly water soluble and osmotically inactive drug (PHCl) was achieved using a solubility modulation approach (Fig. 2). It was observed that in an asymmetric coating of 3 % w/v of ethylcellulose over NaCl, the release of NaCl (which would create a molar environment for PHCl in the asymmetric membrane capsule) was 91.4 mg/mL in 6 h. This meant that an amount of CR NaCl (360 mg), which would release 91.4 mg/mL every 6 h to create 1.50 M molar environment for PHCl should be incorporated in the AMC for controlled release of PHCl from the AMC for 24 h.

Characterization of CR NaCl

The CR NaCl crystals were found to have good flow characteristics with respect to the angle of repose and Hausner ratio. The release profile of CR NaCl crystals (Fig. 3) was used for the selection of optimized coating of ethylcellulose.

Scanning Electron Microscopy (SEM)

Scanning Electron Micrographs (SEMs) of the capsule walls (in Fig. 4) was used to demonstrate the asymmetry of the polymeric capsular membrane. Asymmetrical membrane composed of a dense and thin outer layer Fig. 4(a) with less or no pore structure and a loose and thick inner layer Fig. 4(b) with pore structure. of polymer solution into a macromolecule gel, a state in which the solvent is in a continuous phase to a state where the polymer The formation of asymmetry in polymeric capsule membrane was a result of phase inversion, transformation is in a continuous phase.

Differential Scanning Calorimetry (DSC)

Analysis of the DSC profiles obtained for pure and physical mixtures of promethazine hydrochloride suggests no interaction between the drug and excipients used in study. Fig. 5 shows the endothermic peak at 220 ± 0.98°C with an enthalpy value of 79.9 mj/mg for pure PHCl (A). An endothermic peak for ethylcellulose (B) and CR NaCl(C) crystals was not observed in the scanning temperature range. A single endothermic peak at 220 ± 1.12°C and 220 ± 0.76°C with an enthalpy value of 28.5 mj/mg and 35.7 mj/mg respectively were observed for the physical mixture of drug and CR NaCl (D) and PHCl with CR NaCl and ethylcellulose (E) respectively, which suggests no interaction between the ingredients of the mixture which, if not so would have resulted in a shift in the endothermic peak.

In Vitro Release Studies

In vitro drug release studies were performed in two groups for the factorial design batches. The first group (group 1) consisted of AMC pure, AMC 1 formulation with all the variables at lower level and AMC 2, AMC 3, AMC 5 with one variable at a higher level and two variables at lower level. Results showed that incorporation of higher amounts of controlled release sodium chloride crystals (AMC 5) resulted not only in development of significant osmotic pressure inside the capsular system but also caused concurrent decrease in solubility of the drug, which resulted in reduced drug release with delayed $t_{50\%}$ (12.81 h) though this release was controlled due to the osmotic pressure generation inside the formulation as compared to AMC 1(12.66 h). When the pore former (glycerol) was at a higher concentration (AMC 3), the release from this formulation was slightly more probably owing to increased pore formation on the membrane during dissolution (Fig. 6). However, this effect (12.98 h) was very insignificant as compared to AMC 5 (12.81 h), which probably shows the importance of controlled release formulation of the osmogen. When ethylcellulose concentration was at a higher level (AMC 2), the release of PHCl from the capsular membrane was constrained (14.48 h) as compared with AMC 1 formulation (12.66 h). The decreased drug release and delayed $t_{50\%}$ from AMC 2 might be due to the increased diffusional path for the drug to transverse before being released into the dissolution medium.

The second group, consisted of AMC pure, AMC 8 formulation with all the variables at higher level and AMC 4, AMC 6, AMC 7 with one variable at a lower level and two variables at higher level. Results showed that when the osmogen as well as the pore former were at higher concentrations (AMC 7) there was an increased drug release with faster achievement of $t_{50\%}$ (12.21 h). This effect might be due to the combination of increased pore formation on the capsule membrane and increased osmotic pressure within the formulation thereby helping in faster but controlled release of drug. When ethylcellulose and pore former were at higher concentrations (AMC 4) drug release was constrained (12.96 h), this effect might be due to the much stronger effect of glycerol in reducing the drug holding capacity of ethylcellulose at a higher concentration inside the formulation due to increased number of pores on the polymer structure as compared to AMC 2 (14.48 h) in group one formulation (Fig. 7).

The presence of higher concentration of ethylcellulose retarded drug release though insignificantly in presence of higher concentration of glycerol as compared to AMC 3 (12.98 hrs) in group one formulation wherein similar amount of drug release occurred with a faster $t_{50\%}$. When ethylcellulose and controlled release osmogen were at higher concentration (AMC 6) much lower drug release and $t_{50\%}$ was observed (14.45 h). This probably was due to the combined effect of ethylcellulose in providing increased barrier between the dissolution medium and the core contents inside the formulation and controlled release osmogen in reducing the solubility of the drug and thereby its release.

Optimization Studies

The release profiles up to $t_{50\%}$ of promethazine hydrochloride from all formulations in the dissolution medium were statistically compared with help of Statistical software (minitab®) with release rate profiles of the theoretical formulation (extra design checkpoint batch), which was obtained by using the polynomial equation. The statistical significance was tested at $P > 0.05$. The best formulation among the nonsignificant pairs of formulations was found to be AMC 5, which gave the value of f_2 (similarity factor) as 85.10 (Fig. 8).

Effect of Agitational Intensity

To study the effect of stirring rate on the drug release profiles, dissolution tests of the optimal formulation (AMC 5) was carried out at stirring rate of 50,100,150 rpm stirring did not significantly affect the release rate of drug (Fig. 9). Thus, the mobility of the gastrointestinal tract may scarcely affect the drug release of the asymmetric capsules. This effect describes the fact that the drug release from the AMCs is probably due to the entry of dissolution medium inside the formulation which in turned is controlled due to the presence of barrier layer (ethylcellulose) and not due to the turbulence in the dissolution medium.

Effect of pH of Dissolution Medium

Release profiles at two different pH medium (pH-1.2 and pH-7.4) were compared (Fig. 10) to establish if any relationship existed between the release profile and pH of the dissolution system. The result showed that the release profiles were independent of the pH of the dissolution medium**.**

Effect of Common Ion and Osmotic Pressure on Drug Release

The *in-situ* formation of delivery orifice, effect of common ion and osmotic pressure on drug release was investigated and is depicted in Fig 11. A colored jet stream of ferric chloride from the capsule in the water medium proved the *in-situ* formation of delivery orifice in the capsule wall for drug delivery (AMC-A). When the capsular with core containing ferric chloride and controlled release sodium chloride crystals was suspended in the water medium, the release however got delayed (AMC-B) as compared to the capsule containing only ferric chloride indicating that controlled release sodium chloride crystals provides the common ion which caused a decrease in the solubility of ferric chloride thus delaying the release from the capsular system. However when the capsule was suspended in hypotonic (AMC-C) and hypertonic media (AMC-D) respectively it showed a release in case of hypotonic media and no release in case where the capsule where suspended in hypertonic media. This indicated that not only an osmotic gradient is necessary for drug release from the system but also that *in-situ* formation of a delivery orifice is possible in the thin structure of asymmetric membrane. The common ion present in core formulation and osmotic pressure created between the system

and the media might play an important role in the initiation of this release mechanism is osmotic pumping.

Kinetics of Release

All the models for selecting the release profile were applied on AMC 5. The best-fit model in case of AMC 5 could have followed first-order, Hixson-Crowell model, and Peppas and Korsmeyer model. While considering the higher correlation coefficient value (R), the release data seem to fit the Peppas and Korsmeyer model better. The drug release data were further analyzed for curve fitting based on Power Law, and the results (AMC 5: n = 0.4694, k = 14.7849 and R = 0.9847) confirmed that the formulation AMC 5 followed Fickian diffusion (n < 0.5)

CONCLUSION

Controlled release asymmetric membrane capsule of promethazine hydrochloride were successfully made. The solubility of highly water soluble drug was modulated by use of solubility modulating agent to be incorporated into an osmotic system. The use of solubility modulating agent could be used to modulate the solubility of highly water soluble drug for controlled release.

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