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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF CARBOPOL-INCORPORATED THERMOREVERSIBLE GELS OF PSEUDOEPHEDRINE FOR RECTAL DRUG DELIVERY

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ABSTRACT

Objectives: The present study describes the preparation and evaluation of a Poloxamer 188 (P188)-based thermoreversible gel using Carbopol 934P (C934P) as a mucoadhesive polymer of pseudoephedrine for enhancing the bioavailability and to avoid the first-pass metabolism.

Materials and Methods: Five formulations (F1-F5) were prepared using cold method. The prepared gels were characterized by pH, drug content, spreadability, mucoadhesive force, gelation temperature, and drug release profile. Thermoreversibility of P188/C934P gel was demonstrated by rheological studies. The drug-polymer compatibility was studied using Fourier transform infrared (FTIR).

Results: The incorporation of carbopol into P188 gel also reduced the amounts of drug released from the gel formulations. FT-IR studies revealed that there are no interactions between the drug and polymers. Drug content of gels was estimated and the results were found to be satisfactory. *In vitro* dissolution studies revealed a good drug release from the gels. The drug release was higher in formulations F4 and F5 and lower in F1, F2, and F3 formulations. The order of drug release was found to be F5>F4>F3>F2>F1.

Conclusion: These findings suggested that developed thermoreversible gels could be used as promising dosage forms to rectal drug delivery for prolonged periods in the management of hemorrhoids.

Keywords: Rectal, Drug release, Mucoadhesive, Thermoreversible gel, Decongestant.

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INTRODUCTION

The concept of mucosal adhesion or mucoadhesive was introduced into controlled drug delivery area in the early 1980s, which is a major part of a novel drug delivery system in recent era some of the potential sites for attachment of any mucoadhesive system [1] utilize the property of adhesion of certain water-soluble polymers to buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route, and gastrointestinal area.

The utilization of mucoadhesive system is essential to maintain an intimate and prolonged contact of the formulation with the rectal mucosa allowing a longer duration for absorption. Thermoreversibility is a property of certain substance to be reversed when cooled and return to a viscous fluid state when exposed to heat [2].

Rectal administration uses the rectum as a route of administration for medication and other fluids, which are absorbed by the rectum blood vessels, a drug that is administered rectally will have a faster onset of action [3]. Rectal route offers a useful, non-invasive alternative route of administration when local or systemic effect is intended. The rectum provides a relatively constant environment for drug delivery that allows a constant steady-state concentration of drug in plasma and partially avoids gastrointestinal absorption difficulties and hepatic first-pass metabolism [4].

Hemorrhoids are enlarged and swollen blood vessels but are found in the lower part of the rectum and anus [5]. Internal hemorrhoids grow within the rectum that is above the pectinate line, a boundary that divides the upper two-thirds of the anal canal from the lower one-third of the said area. Internal hemorrhoids are encased in a lining called mucosa that is not sensitive to touch, pain, stretching, or temperature.

Pseudoephedrine shrinks swollen mucous membrane, reduces tissues hyperemia, edema, and congestion. Thus, it provides a decongestant effect indicated for the treatment of hemorrhoids. It is a sympathomimetic amine and vasoconstriction acts on α- and β2-adrenergic receptors, to cause vasoconstriction and relaxation of smooth muscle in the muscles lining the walls of blood vessels.

MATERIALS AND METHODS

Chemicals and reagents

Pseudoephedrine was obtained as a gift sample from Strides Arcolab, Bangalore. Poloxamer 188 (P188) and Carbopol 934P (C934P) were purchased from Sigma-Aldrich.

Formulation of thermoreversible gels

Thermoreversible P188 gels were prepared by the cold method as reported [6]. As shown in Table 1, P188 was dissolved in deionized distilled water (DDW) including drug at room temperature, and it was stored at 4°C for complete solubilization of P188. Carbopol solubilized in DDW was then slowly added to prepared solution with continuous agitation at 4°C. All other excipients such as methylparaben and phosphate buffer were added with continuous stirring. Then, it was kept at 4°C for 24 h before their use. The composition of developed gel formulations is summarized in Table 1.

Determination of pH

The pH of various gel formulations was determined using digital pH meter. 1 g of emulgel was dissolved in 100 ml distilled water and stored for 2 h. The measurement of pH of each formulation was done in triplicate.

Visual appearance and clarity

The clarity and appearance of various developed formulations were determined by visual inspection under black and white background.

Drug content

It is used to measure the content uniformity. 1 ml of formulation was taken and it was added to 10 ml volumetric flask, and then, the volume

was made with distilled water and then further dilutions were made and ultraviolet (UV) absorbance was taken at 255 nm. The blank was prepared by preparing formulation without drug, and then, 1 ml from that was taken and it was added to 10 ml volumetric flask and serial dilutions were made with distilled water, and then, the UV readings were taken, the values obtained were used to calculate the concentration of drug in formulation [7].

Spreadability

For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 200 g weight for 5 min weight was added to the pan. The time in which the upper glass slide and moves over to the lower plate was taken as measure of spreadability [8].

$$S = \frac{ML}{T}$$

Where, M=Weight tide to upper slide, L=Length moved on the glass slide, T=Time taken.

Gelation temperature

Gelation temperature was determined using the tube tilting method [9]. 10 ml aliquot of gel was transferred to test tubes, immersed in a water bath at 4°, and sealed with aluminum foil. The temperature of water bath was increased gradually and left to equilibrate for 5 min at each new setting. The samples were then examined for gelation, which were said to have occurred when the meniscus would no longer move on tilting through 90°. For each solution, the temperature at which a solid gel formed was measured using a calibrated thermometer. All gelation temperature results are the mean of n=3 experiments.

Table 1: Composition of thermoreversible gels of pseudoephedrine

Ingredients	F1	F2	F3	F4	F5
Pseudoephedrine (% W/V)	0.3	0.3	0.3	0.3	0.3
Poloxamer (P188) (% W/V)	18	19	20	21	22
Carbopol (C934P) (%W/V)	0.01	0.02	0.03	0.04	0.05
Methylparaben (%w/v)	0.01	0.01	0.01	0.01	0.01
Phosphate buffer (ml)	10	10	10	10	10

Viscosity studies

Viscosity of the prepared formulations was measured using Brookfield Viscometer. The suitable spindle was lowered perpendicularly into the fixed volume of gel which was to be measured. The spindle was rotated at varying speeds and the suitable speed was selected. The temperature was increased initially >40°C, and then, the viscosity was measured as the system was allowed to cool gradually [10].

Determination of mucoadhesive force

A section of skin membrane (i.e., obtained from rats) and instantly fixed with mucosal side out onto each class vial using rubber band. The vial with membrane was connected to the balance in inverted position while the first vial was placed on a height adjustable pan. The area of tissue surface exposed out is 0.785 cm^2. Then, a height of the second vial was so adjusted that the mucosal surfaces of both vials come in intimate contact. 2 min time of contact was given. Then, weight was kept rising in pan until vials get detached. Mucoadhesive force was the minimum weight required to detach to vials [11].

$$\text{Detachment stress} = \frac{mg}{A}$$

Where, m is the weight added to the balance in grams, g is the acceleration due to gravity taken as 980 cm/s^2, and A is the area of the exposed tissue surface.

***In vitro* drug release studies**

The *in vitro* release of pseudoephedrine from the formulation was studied through egg membrane using modified apparatus. The egg membrane previously soaked for 17 h in phosphate buffer. Then, the

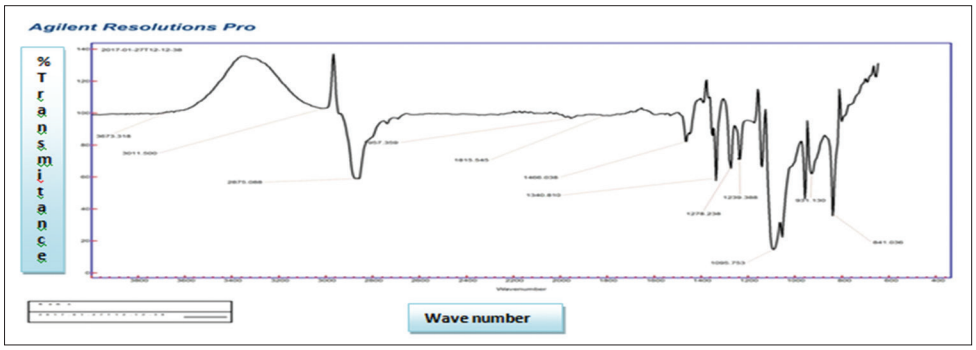

Fig. 1: Fourier transform infrared spectra of drug (pseudoephedrine)

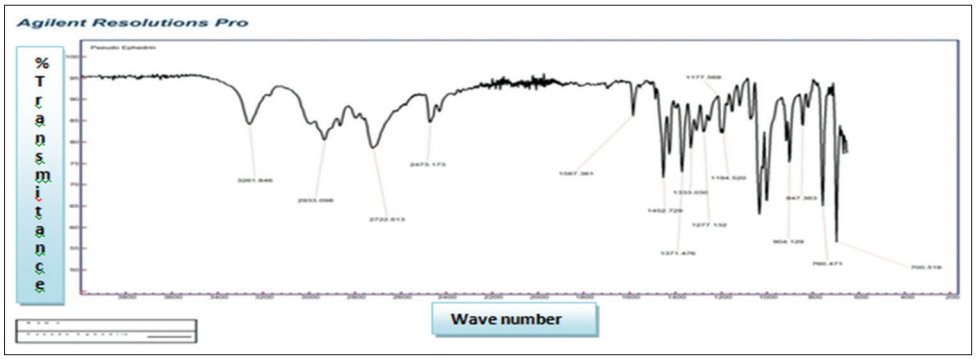

Fig. 2: Fourier transform infrared spectra of polymer (poloxamer)

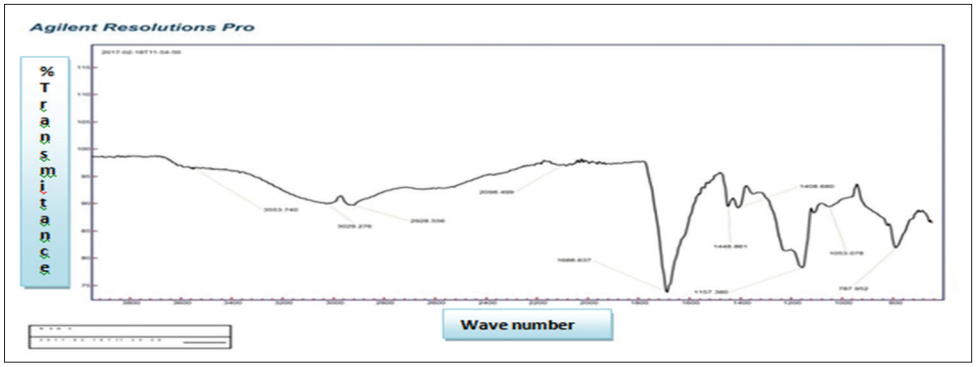

Fig. 3: Fourier transform infrared spectra of polymer (carbopol)

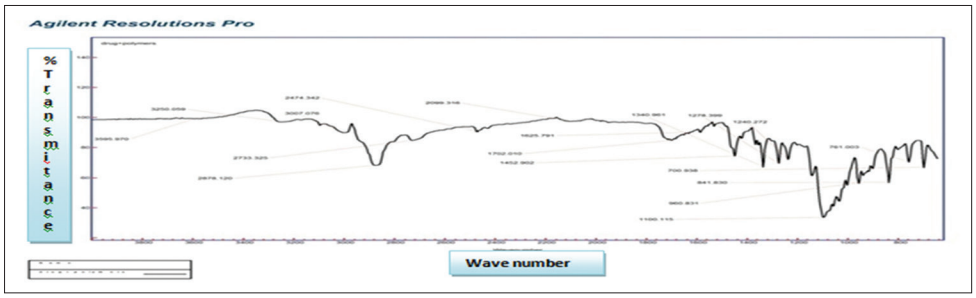

Fig. 4: Fourier transform infrared for pseudoephedrine + polymers

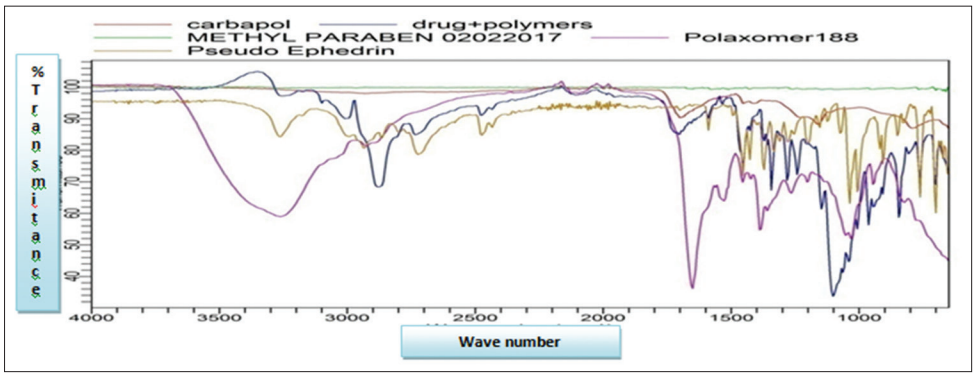

Fig. 5: Fourier transform infrared overlay

Table 2: Appearance, % drug content, and pH of different formulae of pseudoephedrine mucoadhesive thermoreversible gels

Formula code	Appearance	% drug content*±SD	pH*±SD
F1	Transparent, colorless	91.88±0.02	6.5±0.33
F2	Transparent, colorless	92.53±0.01	6.5±0.31
F3	Transparent, colorless	94.69±0.03	6.7±0.32
F4	Transparent, colorless	95.28±0.05	6.8±0.35
F5	Transparent, colorless	97.36±0.07	6.8±0.34

SD: Standard deviation, *Each result is the mean of three determinations±SD

membrane was tied to one end of specially designed glass cylinder. 1 ml of formulation was accurately placed into this assembly. The cylinder was attached to a stand and suspended in 50 ml of dissolution medium maintained at 37+1°C so that the membrane just touched the receptor medium surface. The diffusion medium was stirred at low speed using magnetic stirrer. 5 ml of volume was withdrawn at 40 min time intervals and replaced by an equal volume of receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-visible spectrophotometer at 255 nm. The values had been subjected to the calculation of release profiles of the drug fitting the best model [12]. The results were shown in Table 4 and Fig. 6.

RESULTS

The Fourier transform infrared (FT-IR) spectra of pseudoephedrine, poloxamer, carbopol, and pseudoephedrine loaded in gel formulation are depicted in Fig. 1-5, respectively. FT-IR spectrum of pseudoephedrine showed characteristic peaks at 3673 cm^{-1} (O-H stretching), 3011 cm^{-1} (Aryl C-H stretching), 2875 cm^{-1} (Alkyl C-H stretching), and 2941 cm^{-1} (C-H stretching), whereas FT-IR spectrum of poloxamer showed characteristic peak at 2933 cm^{-1} (Aryl C-H stretching) and carbopol showed characteristic peak at 1606 cm^{-1} (C=O stretching).

The surface pH of the rectal gels was determined to optimize the drug permeation. All tested formulations showed a pH range from 6.5±0.32 to 6.8±0.35 which is acceptable for administration in the rectal cavity. Results are shown in Table 2. The drug content was found to be in acceptable range for all the formulations. Percent drug content in all formulations was in the range of 91.88±0.02–97.36±0.07% indicating uniform distribution of drug. The results are shown in Table 2. All

Table 3: Gelation temperature, mucoadhesive force, spreadability, and viscosity of pseudoephedrine thermoreversible gels

Formula code	Gelation temperature (°C)±SD	Mucoadhesive force* (10^3 dyne/cm^2)±SD	Spreadability *(g cm/s)±SD	Viscosity (C_p±SD)
F1	34.5±0.04	13.37±0.01	31.5±0.02	10400±0.25
F2	35.3±0.01	14.35±0.08	30.2±0.04	11200±0.15
F3	35.9±0.01	17.19±0.04	28.5±0.01	12000±0.38
F4	33.2±0.05	18.16±0.05	25.5±0.05	12500±0.45
F5	32.4±0.02	19.42±0.03	22.2±0.03	15400±0.55

C_p: Centipoise, SD: Standard deviation

Table 4: Comparative *in vitro* drug release studies

S. No.	Time (min)	Drug release*(%)±SD				
		F1	F2	F3	F4	F5
1	40	21.19±0.24	20.23±0.11	19.22±0.22	18.55±0.29	18.23±0.29
2	80	32.09±0.35	32.65±0.21	31.04±0.51	28.65±0.21	27.25±0.22
3	120	49.04±0.40	45.12±0.36	42.89±0.33	38.85±0.33	37.45±0.33
4	160	72.27±0.33	70.78±0.55	69.64±0.20	62.95±0.52	60.45±0.15
5	200	85.87±0.29	82.86±0.64	80.71±0.39	72.55±0.50	70.91±0.50

SD: Standard deviation

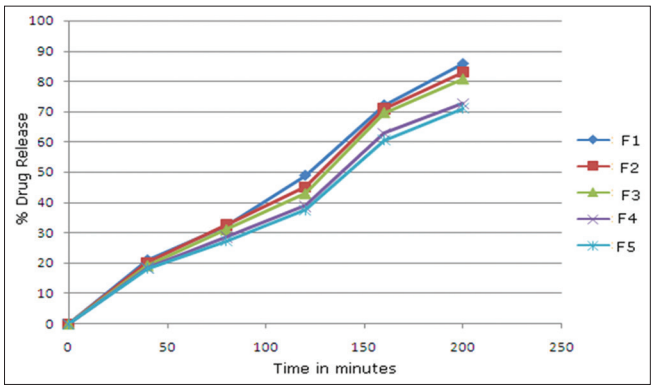

Fig. 6: Drug release profile for the formulations

tested formulations were homogenous, transparent, and colorless. The results are given in Table 2.

The gelation temperature is the criteria for analyzing the properties of a thermoreversible gel. The gelation temperature corresponds to the temperature at which the solution converts to gel. All the formulations exist as liquids at 20.0°C. Gelation temperature for all above five formulations was in the range of 32±0.01–35±0.05°C. The results are given in Table 3. The mucoadhesive strength of the prepared gels was significantly ($p<0.05$) affected by polymer type and it was found that the mucoadhesive strength was significantly ($p<0.05$) increased by increasing the polymer concentration (F4 and F5) compared with F1, F2, and F3, respectively. The spreadability of the prepared gels was significantly ($p<0.05$) decreased as the polymer concentration increased (F4 and F5) compared with F1, F2, and F3, respectively. The viscosity of mucoadhesive gels is expected to affect their retention and spreading at the rectum. Higher viscosities would minimize the problem of seepage of the product which can cause discomfort to the patient. The viscosity ranges of all formulations are 10400±0.25–15400±0.55 centipoises at 25°C. Results are shown in Table 3.

In vitro drug release studies of various formulations were performed using phosphate buffer 6.8 as the diffusion medium and the drug concentration was measured spectrophotometrically at 255 nm. The drug release was higher in formulations F4 and F5 and lower in F1, F2, and F3 formulations. The order of drug release was found to be F5>F4>F3>F2>F1.

DISCUSSION

Pseudoephedrine is a decongestant indicated for the treatment of hemorrhoids. The present work is an attempt to formulate the drug in the form of mucoadhesive thermoreversible rectal gel. Estimation of pseudoephedrine was carried out by UV spectroscopy at 255 nm in phosphate buffer (pH 6.8). Poloxamer acts as thermoreversible polymer, carbopol acts as good mucoadhesive polymer, and methylparaben acts as preservative. The prepared gels were evaluated for their physicochemical parameters such as pH, drug content, spreadability, mucoadhesive force, gelation temperature, and viscosity studies. FT-IR studies reveal that there were no interactions between drug and polymers. Viscosity studies showed that as the concentration of the polymer increased, there was a corresponding increase in the viscosity. All the formulations appeared to have good mucoadhesive strength. This may be due to the fact that increasing the polymer concentration may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in enhancing of mucoadhesive strength [13]. The spreadability of the prepared gels was significantly ($p<0.05$) decreased, this is due to the fact that an increase in polymer concentration increases the repulsion between chains, increases the cross-linking between chains, and reduces the spreadability [14]. The drug content of gels was estimated and the results were found to be satisfactory. *In vitro* dissolution studies revealed a good drug release from the gels. It was found that the drug release was sustained as the polymer concentration increases in the formulation which indicates that the drug release from gels depends on the polymer ratio.

CONCLUSION

A P188-based thermoreversible gel containing C934P (for mucoadhesiveness) was prepared for rectal delivery of pseudoephedrine. The thermoreversibility of P188/C934P gel was verified by various studies. According to the results of *in vitro* drug release studies and depending on the gelation temperature, mucoadhesive force, viscosity, and spreadability, the formulations F4 and F5 showed a significant decrease in drug release rate *in vitro* after 3 h. All of these results revealed that developed thermoreversible gel can be a promising rectal dosage form for the treatment of hemorrhoids and could be subjected for further clinical studies.

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AUTHORS' CONTRIBUTIONS

Padmasree K, Sravani N, Hemalatha A, and Vennelarani Y carried out literature survey and performed the experiment. Mr. Firoz S supervised the work. Mrs. Padmini K and Mr. Firoz S analyzed spectral data and wrote the manuscript. All authors read, reviewed, and approved the final draft of the manuscript before submission.

CONFLICTS OF INTEREST

Authors declare that there are no conflicts of interest.

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