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آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Formulation development and rheological studies of palatable cefetamet pivoxil hydrochloride dry powder suspension

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ABSTRACT

Background and the purpose of the study: Because of its intense bitter taste and susceptibility to moisture Cefetamet Pivoxil (CPH) is presently available only in the form of tablet. The aim of this study was to develop taste masked CPH dry powder suspension.

Methods: Methods employed for formulations were: a) Film coating of CPH using Eudragit E100 and subsequent adsorption on different carriers such as spray-dried lactose, sodium starch glycolate and spray-dried mannitol and b) Complexation of CPH with three different ion exchange resins indion 234 amberlite IRP64 and amberlite IRP69.

Results: Taste viz evaluation as recognized by volunteers revealed that coating with Eudragit E100 and subsequent adsorption on different carriers do not mask the bitter taste of the drug. Suspensions prepared using amberlite IRP64 and amberlite IRP69 were extremely palatable with no bitter after taste. They showed pseudoplastic flow behavior and were too viscous even after shearing for sufficient duration of time and exhibited poor pourability. The suspension made with indion 234 was palatable with slight or no bitter after taste. It demonstrated plastic flow with negligible thixotropy. It had moderate viscosity at rest and could be poured after a reasonable amount of shaking. CPH dry powder suspensions were very unstable under different conditions except under refrigeration. A 5% degradation of drug was occurred in reconstituted suspension in 4 days period when stored at room temperature.

Conclusion: Dry powder suspension prepared with indion 234 having 5% overages was stable even after 4th day of reconstitution and palatable with slight or no bitter after taste.

Keywords: Complexation, Indion 239, Thixotropy, Eudragit E100.

INTRODUCTION

Cefetamet pivoxil hydrochloride (CPH, Fig 1) is an oral third generation cephalosporin antibiotic. The active form of the CPH is cefetamet which is formed invivo by hydrolysis (1). Cefetamet has excellent invitro activity against major respiratory pathogens like Streptococcus pneumoniae, Haemophilus influenzae, β-haemolytic streptococci, Neisseria gonorrhoeae, Enterobacteriaceae and H. influenza (2). It is effective in the treatment of otitis media, pneumonia and in pharyngotonsilitis (3). CPH is also used in the treatment of both upper and lower community acquired respiratory tract and complicated urinary tract infections in children and elderly patients (4).

Presently CPH is formulated and marketed only in the form of tablet because of its intensive bitter taste and instability when stored in liquid form (5). In general better patient compliance in the case of pediatrics and geriatrics can be achieved if the drug is formulated as a liquid dosage form. However formulation of liquid suspension of CPH is not advisable because of its instability in the presence of water (6). So, development of stable and palatable dosage form of CPH is a real challenging job.

In the present work a well known film coating agent Eudragit E100 (7) and three cationic resins viz., indion 234 (8), amberlite IRP64 (9) and amberlite IRP69 (10) were evaluated for their abilities to improve the palatability of CPH and its protection against adverse atmospheric conditions. They are high molecular weight cross-linked polymers and therefore not absorbed by body tissues and are totally safe for human consumption (11). It is well documented that the complexation of drugs with these polymers are stable at the pH of saliva i.e., 6.7 and at cation concentration (40 mEq/l) of saliva. At the same time the complex is weak enough to be broken down at the pH 3 or lower (pH of the stomach). Thus the complexation of drug with these polymers and its development into a dry powder suspension was considered to give a stable and
palatable for the perception of the tongue (12).

MATERIAL AND METHODS

Materials

CPH (Alembic Ltd. Vadodara, India), indion 234, amberlite IRP64 and amberlite IRP69 (Recon Ltd. Bangalore, India) were received as gift samples. Eudragit E100 was supplied by Corel Pharma-Chem. All other chemicals used in the study were laboratory grade.

Methods

Incompatibility studies

Drug and excipients of the formulation were analyzed for compatibility using thin layer chromatography (TLC) technique. Drug and excipients were mixed at 1:1 ratio and stored for 3 months in glass vials at 50°C. Samples were analyzed after 24 hrs and at the end of 3 months storage. Ten microliter of samples dissolved in methanol was applied on thin plate of silica gel GF254 and chromatogram was developed using a mobile solvent system consisting a mixture of benzene, methanol and ammonia (30:10:1). TLC was examined under UV light at 254 nm and R<sub>f</sub> values were calculated using the formula, 

\[ R_f = \frac{\text{Distance travelled by the compound}}{\text{Distance travelled by the solvent front}} \]

Preparation of CPH microspheres

Eudragit E100 was dissolved in 200 ml of the mixture of ethanol and water (6:4). The drug was previously passed through sieve #100 and dispersed into polymer solution by heating on the water bath. Thirty grams of carrier, spray-dried lactose, sodium starch glycolate (SSG) and spray-dried mannitol were added in three separate batches. The whole mixtures was mechanically stirred for 10 min at the speed of 900 rpm using a stirrer (RQ-127A) fitted with a 4-blade impeller. The resulting CPH-polymer carrier adsorbate was air-dried at ambient temperature in the laboratory for 24 hrs and conditioned over calcium sulphate granules (Drierite(R)) in a desiccator overnight and passed through sieve #30 to give free flowing microspheres (13).

Preparation of CPH granules

Complexation of CPH with resins was carried out at different drug to resin ratio (1:1, 1:2, 1:3, and 1:4) for all resins. Resin was added in to water and stirred on magnetic stirrer for 30 min and left to equilibrate for another 30 min to obtain resin slurry. Aqueous drug dispersion was added in small quantities to the resin slurry and stirred continuously at 600 rpm for 4-5 hrs (14). The drug resin complex (DRC) thus obtained was washed on buchner funnel with 500 ml deionized water to remove unbound drug. Washings were digested with known amount of acetonitrile. The concentration of unbound drug was estimated by the analyses of washings by HPLC and drug-loading efficiency was calculated. DRC was dried at 50°C in an oven for 24 hrs or until granular residual moisture content falls to 5%. The DRC was milled and sifted through sieve #60 to obtain free flowing granules.

Dry powder suspension (DPS) formulation

Microspheres and granules prepared above were blended separately with the ingredients shown in table 1 for 10-15 min. Formulations (8 doses) were filled into amber colored bottles, labeled and stored between 2-8°C till further studies. DPS was reconstituted by addition of 40 ml of purified water with agitation.

Assay

The drug content of 1) CPH-polymer-carrier 2) CPH-resin complex 3) DPS and 4) reconstituted suspension (RS) on the days of 1 and 4 were determined by HPLC method (15) using Shimadzu CLASS-VP V6.12 SP4 chromatograph equipped with Inertsil, ODS, C<sub>18</sub>, 150x4.6 mm, 5 µ column. The chromatogram was obtained by injecting 20 µl of the solution of CPH in acetonitrile and water mixture (1:1). The flow rate was adjusted to 1 ml/min and UV-Visible spectrophotometer set to 264 nm was used as detector. The calibration curve was found to be linear ($R^2=1$) at the concentrations of 25 and 200 µg/ml. The calibration curve of CPH in 0.1N HCl which was developed using UV-Visible spectrophotometer at 264 nm showed linearity from 4 µg/ml to 24 µg/ml. The working curve equation was $y=0.0329x$ with correlation coefficient value of, $r^2=0.9999$. Solutions were sonicated and filtered through 0.45 µ (Millipore) membrane filter prior to analysis.

Physical properties

Powder properties (16) were measured for DPS using tap density tester (Electrolab ETD-1020). The angle of repose was measured by fixed cone method. pH of RS was measured on the days of 1 and 4 at 25°C using a digital pH meter. The specific gravity (Sp.gra) of the RS was determined in a specific gravity bottle at 25°C using following formula, 

\[ \text{Sp.gra}=\frac{\text{Weight of the RS}}{\text{Weight of an equal volume}} \]
Cefetamet Pivoxil Dry Powder Suspension

Dissolution studies

Dissolution studies (17) were performed for a total period of one hour in USP 24 type-II (Paddle method) apparatus at 50 rpm. DPS equivalent to 200 mg of CPH was transferred to 500 ml of 0.1N HCl solution maintained at 37±0.5°C and 5ml sample was withdrawn at regular intervals during one hour, replaced with the same volume of prewarmed (37±0.5°C) fresh dissolution medium and were analyzed using UV-Visible spectrophotometer.

Palatability test

The gustatory sensation tests were performed in six healthy human volunteers (20-25 years). The test was approved by the institutional human experimentation committee (Proposal No. VIPS/872/2/09-10).

To find a suitable concentration for the evaluation of the bitterness intensity during the comparative test, 6 standard dispersions of drug in water at concentrations of 0, 10, 20, 30, 40 and 50 µg/ml were prepared. Human volunteers were asked to hold 5 ml of aqueous dispersion of CPH in their mouth and bitterness recognition threshold of pure drug was evaluated (18). The bitterness level of RS was recorded against standard dispersions of drug using a numerical scale (19). Human volunteers were asked to taste 5 ml of RS. Then, they were required to give one of these graded perceptions; Palatable with no bitter after taste=0, Palatable with slight bitter after taste=1, Quite palatable with bitter after taste=2 and Very unpalatable with bitter after taste=3.

Rheological studies

The sedimentation volumes were determined for 50 ml of each suspension at intervals of one day and up to seven days. The sedimentation volume F (%), was calculated using the formula F=100Vu/Vo, where Vu is the volume of the sediment and Vo is the original volume.

The rheological studies were conducted for 8 ml of RS at 25°C using Brookfield DV-II+ Pro EXTRA viscometer with spindle SC4-18. Spindle speed was varied for ascending and descending modes by change of 10 rpm/min. Rheograms were constructed and rheological properties were measured (20, 21).

Stability studies

DPS and RS of F4, F5 and F6 were subjected to stability studies. Formulations were packed and sealed in amber colored glass bottles and kept for one month storage at 28±2°C, 40±2°C, 50±2°C, 60±2°C and under refrigeration condition of 2-8°C at ambient humidity conditions. Preparations were analyzed for the change in drug content and appearance at periodic intervals of time for 1, 2 and 4 week. FTIR analysis was also employed to quantify interaction between indion 234 and CPH using Shimadzu 8400S FTIR spectrophotometer (Kyoto, Japan).

Table 1. Formulation of CPH dry powder suspension.

| Formulation ingredients                  | F1   | F2   | F3   | F4   | F5   | F6   |
|------------------------------------------|------|------|------|------|------|------|
| Cefetamet pivoxil hydrochloride          | 1.6  | 1.6  | 1.6  | 1.6  | 1.6  | 1.6  |
| Eudragit E100                            | 2    | 2    | 2    | -    | -    | -    |
| Spray dried lactose                     | 3    | -    | -    | -    | -    | -    |
| Sodium starch glycolate                  | -    | 3    | -    | -    | -    | -    |
| Spray dried mannitol                     | -    | -    | 3    | -    | -    | -    |
| Indion 234                               | -    | -    | -    | 4.8  | -    | -    |
| Amberlite IRP64                          | -    | -    | -    | -    | 4.8  | -    |
| Amberlite IRP69                          | -    | -    | -    | -    | -    | 4.8  |
| Avicel CL611                             | 1.2  | 1.2  | 1.2  | -    | -    | -    |
| Aspartame                                | 0.3  | 0.3  | 0.3  | 0.18 | 0.18 | 0.18 |
| Monobasic sodiumphosphate                | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 |
| Dibasic sodium phosphate                 | 0.42 | 0.42 | 0.42 | 0.42 | 0.42 | 0.42 |
| Bronopol (dried)                         | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 |
| Trusil orange flavor                     | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Methyl paraben                           | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Propyl paraben                           | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |

*a All quantities are in grams

*b Drug to resin (D:R) ratios for F4, F5 and F6 were 1:3
RESULTS AND DISCUSSION

Formulation development

In this investigation different formulations of CPH were developed using various excipients to mask their bitter tastes. All excipients selected for the formulation were compatible with the drug as it was confirmed by the $R_f$ values of TLC studies (Table 2). Microspheres of CPH prepared using eudragit E100 and subsequent adsorption on different carriers were uniform, smooth in their surfaces and were free flowing as evident from the flow properties shown in Table 3. Granules prepared with resin were irregular in shape, hard, and rough in texture depending to resin concentration and showed average flow property and poor packing arrangement (Table 3). Drug-resin ratio of (D:R) of 1:3 was found to be the minimum for giving maximum drug loading efficiency with moderate viscosity. The formulations made with amberlite IRP64 and amberlite IRP69 had relatively higher viscosities even at 1:3 (D:R) ratios. Further, these preparations were slightly brown colored due to the color of the resin itself.

Drug content of DPS and RS on the first day found to be 96.23 to 98.45% respectively. The drug release from all formulations were 90% or higher within 5 min (Fig 2) which confirms that complexation process does not affect the release of drug from DRC at the pH of stomach.

For all formulations, pH were maintained above 6 and specific gravity were within the desired range (>1) even after 4th day of reconstitution which confirms that DPC was intact during storage period (Table 4).

Palatability test

The perception and bitterness recognition of pure drug from the majority of volunteers was found to be 50 µg/ml. Taste evaluation (Table 5) as recognized by volunteers revealed that coating with Eudragit E100 and subsequent adsorption on different carriers does not mask the bitter taste of the drug. Microspheres adsorbed on to mannitol were relatively palatable with bitter after taste and compared to drug-resin-complex

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**Table 2.** $R_f$ values of mixture of CPH and excipient determined by TLC study.

| Component (1:1 mixture)         | $R_f$ values (After 24 hrs) | $R_f$ values (After 3 months) |
|---------------------------------|-----------------------------|-------------------------------|
| Pure CPH                        | 0.673                       | 0.67                          |
| CPH + Spray dried lactose       | 0.64                        | 0.65                          |
| CPH + SSG                       | 0.67                        | 0.66                          |
| CPH + Spray dried mannitol      | 0.65                        | 0.65                          |
| CPH + Eudragit E100             | 0.672                       | 0.668                         |
| Drug + Indion 234               | 0.671                       | 0.66                          |
| CPH + Amberlite IRP64           | 0.65                        | 0.66                          |
| CPH + Amberlite IRP69           | 0.64                        | 0.65                          |
| Drug + Myristic acid            | 0.669                       | 0.659                         |
| Drug + Bronopol                 | 0.67                        | 0.671                         |
| Drug + Aspartame                | 0.65                        | 0.645                         |
| Drug + Sucrose                  | 0.675                       | 0.653                         |
| Drug + Tutti fruti flavor       | 0.66                        | 0.67                          |
| Drug + Propyl paraben           | 0.67                        | 0.66                          |
| Drug + Ethyl paraben            | 0.67                        | 0.65                          |

*Values are average of 3 determinations (n=3)

**Table 3.** Powder properties and assay values for dry powder suspension.

| Physical properties       | Formulation code | F1 | F2 | F3 | F4 | F5 | F6 |
|---------------------------|------------------|----|----|----|----|----|----|
| Bulk density (g/cc)       |                  | 0.550 | 0.567   | 0.574   | 0.541   | 0.553 | 0.564 |
| Tapped density (g/cc)     |                  | 0.561 | 0.734   | 0.719   | 0.721   | 0.715 | 0.717 |
| Carr’s index              |                  | 18.95 | 18.94   | 18.88   | 19.21   | 19.22 | 20.07 |
| Hausner ratio             |                  | 1.24  | 1.232   | 1.234   | 1.226   | 1.231 | 1.219 |
| Angle of repose, $\theta$ |                  | 24.70$^\circ$ | 26.27$^\circ$ | 28.33$^\circ$ | 24.40$^\circ$ | 23.40$^\circ$ | 25.40$^\circ$ |
| Assay of dry powder suspension (%) |        | 97.23 | 97.09   | 96.23   | 98.15   | 98.45 | 97.15 |

*Values are average of 3 determinations (n=3)*
Table 4. Physical characteristics of reconstituted suspension.

| Formulation code | Sedimentation volume % | pH of the formulation | Specific gravity | Results of the assay of formulation (%) |
|------------------|-------------------------|-----------------------|-----------------|-----------------------------------------|
|                  | Day 1 | Day 7 | Day 1 | Day 4 | Day 1 | Day 4 | Day 1 | Day 4 | Day 1 | Day 4 |
| F1               | 57    | 51    | 6.21  | 6.25  | 1.22  | 1.19  | 97.13 | 91.01 |
| F2               | 59    | 50    | 6.16  | 6.14  | 1.13  | 1.12  | 97.08 | 92.81 |
| F3               | 56    | 52    | 6.21  | 6.12  | 1.03  | 1.01  | 96.02 | 91.14 |
| F4               | 59    | 54    | 6.72  | 6.63  | 1.53  | 1.48  | 98.02 | 93.12 |
| F5               | 63    | 63    | 6.83  | 6.67  | 1.76  | 1.73  | 98.25 | 92.35 |
| F6               | 67    | 65    | 6.79  | 6.68  | 1.78  | 1.74  | 97.15 | 91.88 |

*Values are average of 3 determinations (n=3)*

Table 5. Bitterness evaluations by taste panel.

| Formulations | Volunteer opinion |
|--------------|-------------------|
|              | 1 | 2 | 3 | 4 | 5 | 6 |
| Pure drug    | 3 | 3 | 3 | 3 | 3 | 3 |
| F1           | 2 | 3 | 2 | 2 | 2 | 3 |
| F2           | 3 | 2 | 2 | 3 | 2 | 2 |
| F3           | 2 | 2 | 2 | 2 | 2 | 2 |
| F4           | 1 | 0 | 0 | 1 | 0 | 1 |
| F5           | 0 | 0 | 0 | 0 | 0 | 0 |
| F6           | 0 | 0 | 0 | 0 | 1 | 0 |

*Values are average of 3 determinations (n=3)*

Figure 2. Dissolution profile of CPH formulations at various times.

were less palatable and therefore were withdrawn from further studies. Suspensions prepared using amberlite IRP64 and amberlite IRP69 were extremely palatable with no bitter after taste and formulation made with indion 234 was palatable with slight or no bitter after taste.

*Rheological studies*

All formulations had high sedimentation volume, which indicated drug particles formed flocs. Rheograms of formulations F4, F5 and F6 are shown in figure 3. The hysteresis loop area indicates the extent of structural breakdown and time for recovery. Formulation F4 demonstrated plastic flow with negligible thixotropy and additionally, no hysteresis effect (Fig 3a). This is due to the possible breakdown in structure which might reform immediately during the flow system. Formulations F5 and F6 showed...
pseudoplastic flow behavior, whose loop areas were relatively high compared to F4 (Fig 3b). Steady shear flow behavior observed with F4 was minimum compared to F5 and F6 formulations as it is shown in figure 3c. This means that subjecting a material to stress less than the yield stress will lead to a nonpermanent deformation. Formulation F4 had moderate viscosity at rest and it could be poured after a reasonable amount of shaking. Formulation F5 and F6 were too viscous even after shearing for sufficient duration of time and exhibited poor pourability.

Stability studies

CPH dry powder suspensions were very unstable under different storage conditions except refrigeration. There were a decrease in drug content by 5 to 10% in all formulations when stored at...
28±2°C for 1 month. A 5% degradation of drug was occurred in RS in 4 days period at room temperature. Hence the formulations of CPH with 5% overages are recommended. FTIR studies confirmed complexation stability of CPH with indion 234 (Fig 4).

CONCLUSIONS
The results of this work showed that microspheres prepared with Eudragit E100 and subsequent adsorption on carriers doesn’t improve palatability of CPH. Formulation with amberlite IRP64 and IRP69 were palatable but had high viscosity upon reconstitution. DPS prepared with resin indion 234 having 5% overages was palatable and stable even after 4th day of reconstitution at room temperature.

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REFERENCES
1. Cefetamet pivoxil HCl. Official monographs for part I, Japanese Pharmacopoeia XIV. 328-329.
2. Hayton WL, Walstad RA, Thurmann-Nielsen E, Kufaaas T, Kneer J, Ambros RJ, Rugstad HE, Monn E, Bodd E, Stoecckel K. Pharmacokinetics of intravenous cefetamet and oral cefetamet pivoxil in children. Antimicrob Agents Chemother, 1991; 35: 720-725.
3. Houl P, Von AG, Jacqueline ZI. Cefetamet pivoxil: Bacteriostatic and bactericidal activity of the free acid against 355 gram-negative rods. Infection, 1988; 16:194-198.
4. Bryson HM, Brogden RN. Cefetamet pivoxil. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drug, 1993; 45:589-621.
5. Stoecckel K, Harell M, Dan M. Penetration of cefetamet pivoxil and cefuroxime axetil into the maxillary sinus mucosa at steady state. Antimicrobial Agents Chemothe, 1996; 40:780-783.
6. Nalinee A, Surapee P. In Vitro Activity of Cefetamet, A New Beta-Lactamase Stable Oral Cephalosporin. J Infect Dis Antimicrob Agent, 1990; 7: 1-3.
7. Paharia A, Yadav AK, Rai G, Jain SK, Pancholi SS, Agrawal GP. Eudragit-coated Pectin Microspheres of 5-Fluorouracil for Colon Targeting. AAPS PharmSciTech, 2007; 8: E1-E7.
8. Harmik S, Yasmin S, Roop KK. Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches. Drug Dev and Ind. Pha., 2004; 30: 429 - 448.
9. Inderbirsingh, Ashish K, Rehni, Rohit K, Gaurav J, Manoj kumar, Hassan Y. Aboul-enein. Ion Exchange
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Resins: Drug Delivery and Therapeutic Applications: Scientific Review. Fabad J. Pharm. Sci, 2007; 32: 91-100.

10. Mahore JG, Wadher KJ, Umekar MJ, Bhoyar PK. Ion Exchange Resins: Pharmaceutical Applications and Recent Advancement. Int. J. Pharm. Sci. Rev. Re, 2010; 1: 8-13.

11. Kudela V. Editor. Encyclopedia of polymer sciences and engineering. New York, John Wiley. 1987.

12. Esposito E, Cortesi R, Luca G, Nastruzzi C. Pectin-Based Microspheres. Annals. New York Acad. Sci. 2006; 944: 160-179.

13. Chang SJ, Cheng-Chie Niu G, Kuo SM, Chen SF, Preparation and preliminary characterization of concentric multi-walled chitosan microspheres. J. Biomed Mat. Research, 2007; 81A: 554-566.

14. Irwin WJ, McHale R, Watts PJ. Drug Delivery by Ion Exchange Part VII: Release of Acidic Drugs from Anionic Exchange Resinate Complexes. Drug Dev and Ind. Pha. 1990; 16: 883-898.

15. Lisoni M. Morsch, Celso F. Bittencourt, Marines J. Souza E, Julie M. LC method for the analysis of cefetamet pivoxil hydrochloride in drug substance and powder for oral suspension. J. Pharm. Bio. Analysis, 2002; 30: 643-649.

16. Niklas S, Katharina R, Jyrki H, Jouko Y. Effect of Moisture on Powder Flow Properties of Theophylline. Pharmaceutics, 2010; 2: 275-290.

17. Gao Z, Moore TW, Smith AP, Doub WH, Westenberger BJ. Studies of variability in dissolution testing with USP apparatus 2. J.Phrm Sci, 2007; 96:1794-1801.

18. Schiffman HS. Sensation and Perception: An Integrated Approach. 5th ed. John Wiley and Sons, Ontario, Canada, 2000; 163-169.

19. Anand V, Kharb V, Kataria M, Kukka V, Choudhury PK. Taste assessment trials for sensory analysis of oral pharmaceutical products. Pak J Pharm Sci. 2008; 21: 438-450.

20. Ramakrishna C, Sripathi K, Sunki Reddy YR. Rheological behavior of syrups containing sugar substitutes. Eur Food Res Tech, 2006; 218: 345-348.

21. Martin A. Physical Pharmacy. Rheology. 4th ed Lippincott Williams and wilkins. Philadelphia, 1993; 561-583.
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مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله