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SYNTHESIS, FORMULATION AND EVALUATION OF CHALCONE AS POTENT ANTIMICROBIAL AGENT

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ABSTRACT

In a wide search program towards new and efficient antimicrobial agent chalcone has been synthesized by condensing benzaldehyde derivatives with acetophenone derivatives in dilute ethanolic sodium hydroxide solution at room temperature according to Claisen Schmidt condensation. Then synthesized compound formulated and evaluated as enteric coated tablets to reduce the gastrointestinal tract side effects. Enteric coat was employed by using different polymers such as HPMC-55, Eudragit and Ethyl cellulose in different ratios. Formulation exhibited optimum dissolution, disintegration, hardness and friability properties. The antimicrobial activity of the novel products were evaluated by Filter Paper Disc diffusion Method. This study concluded that enteric coated tablets of chalcone can be prepared by using combination of polymers with optimum quality control parameters which ultimately reduces the GI tract side effects and retained its potency as antimicrobial agents.

KEY WORDS

Chalcone, HPMC-55, Ethyl cellulose and Antimicrobial agent.

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INTRODUCTION

There is growing interest in the pharmacological potential of natural products is chalcone constitute an important group of natural products. Chemically, they consist of open chain flavanoids in which the two aromatic rings are joined by a three carbon α-β unsaturated carbonyl system The presence of a reactive α-β unsaturated keto function in chalcones is found to be responsible for their antimicrobial

activity[1]. In recent years a variety of chalcones have been reviewed for their cytotoxic, anticancer chemoprevenive and mutagenic as well as antiviral, insecticidal and enzyme inhibitory properties[2,3].

Chalcone reported to have GI side effects thus this article presents formulations of enteric coated tablets which releases the drug only in alkaline pH near 6.8. This leads to cross GI side effect. Different ratios of polymers (HPMC-55, Eudragit, Ethyl cellulose) in combination selected for the purpose. Within this study it was found that ethyl cellulose and HPMC-55 gives a promising results[4-6]. The antimicrobial activity of the formulations was evaluated by Filter Paper Disc diffusion Method. This study concluded that enteric coated tablets of chalcone reduce the GI tract side effects and retained its potency as antimicrobial agents.

MATERIALS AND METHODS

HPMC–55 procured from USV limited, Govandi, Mumbai. Ethyl cellulose, magnesium stearate, talc, polyvinyl chloride procured from local chemical market. All other ingredients used were of pure grade.

General Procedure

Chalcones were synthesized by base catalyzed Claisen-Schmidt condensation reaction of acetophenones and aldehydes by known literature method[7]. A mixture of benzaldehyde (0.01 mol) and acetophenone (0.01 mol) was dissolved in 10 ml rectified spirit in a 250 ml round-bottomed flask equipped with a magnetic stirrer. Then 10 ml NaOH solution (1g in 10ml H_2O) was added drop wise to the reaction mixture on vigorous stirring for 30 minutes when solution became turbid. The reaction temperature was maintained between 20-25^{0}C using a cold water bath on the magnetic stirrer. After vigorous stirring for 4-5 hours the reaction mixture was neutralized by 0.1-0.2 N HCl whereby the precipitation occurred. On filtering off, the crude chalcone was dried in air and recrystallized by rectified spirit. The residue was purified on column chromatography (silica gel with 10% ethyl acetate in hexane) to afford pure chalcone (Figure No.1).

Preparation of core tablets[8,9]

The core tablets were prepared by direct compression method. All the ingredients were mixed and passed through sieve no. 60 to get uniformly distributed and uniform sized particles. Then after sieving process the mixture is put for the compression on tablet punching machine using biconvex round shape die and punches. Detailed composition of tablets is given in Table No.1.

Preparation of enteric coated tablets[8-10]

The composition of a core tablet is same the coating polymers were different (HPMC- 55, Ethyl cellulose, Eudragit) and different ratios as given in Table No.2.

EVALUATIONS OF ENTERIC COATED TABLETS

Hardness

The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, was recorded.

Friability

Tablet strength was tested by Roche Friabilator. Preweighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets.

Uniformity of weight

Randomly selected twenty tablets from all the formulations were weighed individually and together on electronic balance. The average weight was noted.

In vitro Dissolution tests

Drug release profile was evaluated *in vitro,* using a dissolution test apparatus. The dissolution of enteric coated tablet is performed into 0.1N HCL for 2 hours and then the phosphate buffer pH 6.8 for 1 hour. The temperature was maintained at 37 ± 0.5°C and a constant paddle rotation speed of 100 rpm. Samples (5 ml) were withdrawn at regular intervals and filtered. The samples were analyzed by UV spectrophotometer at wavelength 276 nm[11].

Antibacterial activity

Antimicrobial activity of all synthesized compounds was determined by disc diffusion method[12]. Human pathogenic bacteria *viz*; *Staphylococcus aureus*, *Pseudomonas aeruginosa* were used. Preparation of

nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Discs measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. Stock solutions of synthesized compounds diluted in dimethyl sulphoxide (1% DMSO) to give final concentration of 500µg/ml and 1000 µg/ml. A reference standard was made by dissolving accurately weighed quantity of chloramphenicol in sterile distilled water. The incubation was carried out at 37ºC for 24h. All the experiments were carried out in triplicate. Simultaneously, controls were maintained by employing 0.1 mL of DMSO which did not reveal any inhibition. Zones of inhibition produced by each compound were measured in mm. The results of antibacterial studies are given in Table No.3.

RESULTS AND DISCUSSION

As mentioned above the chalcone is having many biological activities but also having side effects which are related with the upper gastrointestinal tract. The purpose of formulation of the enteric coated tablets of chalcone is to delay the release of drug and to allow release in lower part of gastrointestinal tract. The reason behind this delaying of release is, to prevent the contact of drug with the upper gastro intestinal tract. Different core tablets were prepared each with varying concentrations of disintegrating agents. The prepared tablets were subjected to disintegration test at pH 6.8 phosphate buffer and the tablet which disintegrated within 3 minutes is selected for further enteric coating (C3). All the other tests like hardness, friability were employed for this core tablet (C3). Enteric coating was applied using various polymers like hydroxyl propyl methyl cellulose phthalate (HPMC -55) and eudragit. The best combination we found that was of ethyl cellulose and HPMC-55 (C2), the coating was remain intact for two hours in the acidic pH 0.1 N HCL and disintegrated completely in the phosphate buffer pH 6.8 within half an hour. Combination HPMC -55 and the eudragit (C3) was not intact more than one and half hour in the 0.1 N HCL, also HPMC-55 (C1)was not remain intact in 0.1N HCL for more than one hour. So, the combination of HPMC -55 and ethyl cellulose (C2) was best for the enteric coating, which has given optimum result in hardness and friability and dissolution within officially specified limits (Figure No.2).

The results of antimicrobial activities revealed that majority of the synthesized compounds showed varying degrees of inhibition against Microbes shown in Table No.3. The all formulations showed excellent activity at both concentration i.e. 100µg/ml and 150 µg/ml. Further it was observed that all formulations retained their potent antimicrobial activity irrespective of their formulations excipient.

Table No.1: Composition of core tablet formulations

S.No	Ingredients (mg)	C1	C2	C3
1	Chalcone	100	100	100
2	Lactose	50	50	50
3	Talc	5	5	5
4	Magnesium stearate	3	3	3

Table No.2: Composition of enteric coating formulations

S.No	Ingredients (mg)	C1	C2	C3
1	HPMC-55	40	40	40
2	Eudragit	-	-	5
3	Ethyl cellulose	-	5	-
4	Talc	1	1	1
5	Magnesium stearate	1.5	1.5	1.5

Table No.3: Antimicrobial activity of the formulations

S.No	Formulations	Antibacterial activity (%inhibition)			
		Staphylococcus aureus	***Pseudomonas aeruginosa***	***Staphylococcus aureus***	***Pseudomonas aeruginosa***
		100µg/ml	**150 µg/ml**	**100µg/ml**	**150 µg/ml**
1	Chalcone	23.2	48.7	23.4	51.2
2	C1	21.2	47.2	22.1	50.4
3	C2	23.0	51.5	23.0	51
4	C3	24.1	50	23.5	52.5
5	DMSO	2.3		3.4	

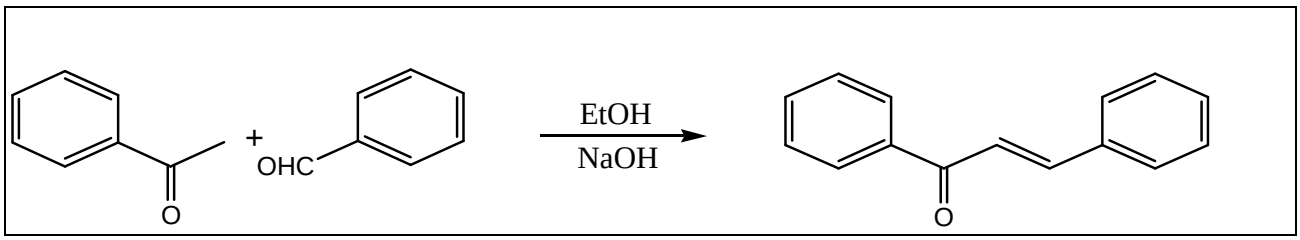

Figure No.1: Scheme for the synthesis of chalcone

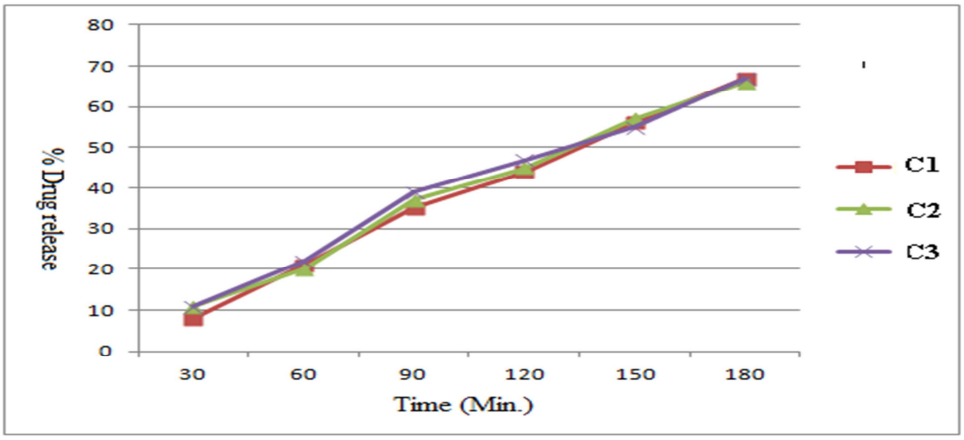

Figure No.2: Dissolution profile of different formulations

CONCLUSION

From all above studied it was concluded that by using combination of HPMC-55 and ethyl cellulose (10:1.5) we can apply effective enteric coat to the rapid disintegrating core table. So, by this way we can prevent the side effects of chalcone in upper gastrointestinal tract. Thus these formulations can be employed commercially as potent antimicrobial agents with reduced G.I. tract ulcerogenic profile.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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