DISSERTATION ABSTRACTS

DESIGN AND PREPARATION OF CONTROLLED RELEASE BEAD FORMS USING NATURAL POLYMERS

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I. SUMMARY

Alginates which are obtained from marine brown algea, are natural polymers that are biocompatible and biodegradable. The use of alginates have received much attention in pharmaceutical preparations, particularly as a vehicle for controlled drug delivery.

Nicardipine HCl has a short biological half life (about one hour) and its absorption is rapid and complete. So, it has a need to evaluate controlled release dosage forms.

It is aimed to prepare alginate-gel beads, which were formed based on the ion exchange between sodium alginate and divalent cations and to investigate the factors, which affect the formulation, in this study.

First, the release profiles of the formulations which were prepared by using alginates with different M/G content and viscosity were compared. The release was extended with the alginates which have high guluronic acid content. Two formulations which gave the most close release profile to target profile were chosen and the effect of the factors which affect the formulations were investigated by 2^3 factorial design. The effect of drug: polymer ratio, $CaCl_2$ concentration, curing time and Na-alginate concentration on the time for 50% of the drug to be released ($t_{50\%}$) and drug entrapment efficiency were evaluated with analysis of variance.

The in vitro release studies were carried out by flow-through cell apparatus at different media.

It was found that, nicardipine: alginate ratio was a significant parameter which affect both the $t_{50\%}$ and drug entrapment efficiency. The release of nicardipine from the alginate beads, which were prepared in a ratio of 1:1, was more extended than those of the 1:2 beads. The drug release from alginate beads in a ratio of 1:1 increased by increasing $CaCl_2$ concentration. But the opposite relationship was observed in the case of 1:2 beads. It was found that curing time was not a significant parameter in $t_{50\%}$ but Na-alginate concentration slightly effects the $t_{50\%}$. It was also seen that Na-alginate concentration did not affect the drug entrapment efficiency; whereas the effect of $CaCl_2$ concentration was significant for the 1:2 beads.

Different polymers were added to the 1:1 beads and the release profiles and kinetics of them were investigated. The release rate of formulation which was prepared by adding chitosan was in most agreement with the target profile. It was seen that the erosion of alginate-gel matrix at pH 7-7.5, was reduced by using chitosan.

Swelling studies showed that the alginate-gel beads swelled slightly at pH 1.2 and 2.5. They reached the maximum swelling ratio at pH 4.5 and then eroded at pH 7-7.5.

The particle size of all formulations was measured with a micrometer and the mean radius and standart deviation were calculated.

Morpohological examination of the surfaces of alginate-beads were carried out using scanning electron microscope (SEM).

In conclusion, the controlled zero order release bead dosage form of nicardipine based on ion exchange between alginate, chitosan and Ca^{++} can be developed.

THE INTERACTION BETWEEN THE METABOLISMS OF CAFFEINE AND THEOPHYLLINE

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ABSTRACT

Interrelationships between the urinary excretion patterns of theophylline and its metabolites were investigated in a subject on routine (600 mg/day) theophylline therapy. High performance liquid chromatographic analysis showed that daily amounts of theophylline and its metabolites excreted were : Theophylline, 14 ± 2.7; 1-methylxanthine (1X), 1.4 ± 0.3; 3-methylxanthine, 11±0.8; 1-methylurate (1U), 14±1.9 and 1,3-dimethylurate (13U), 35±1.9 mole percent of the dose. Total daily recovery was 76±4 %. Linear regression analysis showed that the highest correlation was between the urinary excretions of 13U and 1U (r= 0.73 ± 0.08) while the poorest correlation was observed between the excretions of 1X and 1U (r = 0.53±0.02). The results suggested that 1U did not derive solely from 1X, implicating 13U as an supplementary source.

The effects of theophylline on the metabolism of caffeine and on the distribution of metabolites in urine were studied by administering a single dose of caffeine (338 mg) in addition to the routine dose of theophylline. The metabolite pool (1,7-dimethylxanthine + 1,7-dimethylurate (17U) + 1X + 1U) reflecting the primary 3-demethylation of caffeine (paraxanthine formation) was found not to be affected by the presence of theophylline. This result suggested that theophylline did not alter the demethylation pattern of caffeine; consequently either theophylline did not undergo 3-demethylation (to yield 1X) or theophylline and caffeine did not share the same 3-demethylation system. The excreted amount of 1X was consistent with previously reported data associated with caffeine metabolism. In contrast the level of 17U was 2-fold higher than expected; the level of the common metabolite of caffeine and theophylline, 1U, was low. This suggested that 1U derived at least partially from 17U and the decrease in 1U level might be caused by competition between 17U and 13U for a common demethylation system.

DISSERTATION ABSTRACTS...

SYNTHESIS OF N-SUBSTITUE INDOLE -2 - CARBOXYLIC ACID DERIVATIVES, INVESTIGATION OF THEIR ANTISPASMODIC AND ANALGESIC ACTIVITIES

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In many countries, different compounds are used in the same drug combination for their analgesic and antispasmodic activities. But in the recent years, in different countries including Turkey, most of the licenced of such drugs are being canceled, because of unexpected and severe side effects of their active ingredients which are appeared particularly when they are in the same combination. In addition to this, there are also some difficulties for analytical control of those drugs when they include more than one active compound.

For these reasons, in our thesis we have aimed to design and synthesis of N-substituted - indol - 2 - carboxylic acid derivatives, which would exhibite both analgesic and antispasmodic activities in the same compound. The investigation of their pharmacological activities was also targeted to be done in the thesis study.

In the synthesis part of our study, we have completed the synthesis of 23 compounds in three different series. Those are;

1-N-benzyl derivatives

2-N-phenyl derivatives

3-N-H derivatives

The structural elucidation of entire compounds were confirmed by TLC, melting point and elementary analysis and UV, IR, ^{1}H-NMR, Mass spectroscopies were also used for this reason.

In order to search the pharmacological activities of synthetised compounds, the MAGNUS Method was performed for the antispasmodic activity by using guinea-pig ileum and the compounds were compared with Atropin.

The tested compounds (S_2, S_{2a}, S_{2b}) were found promising for antispasmodic activity and they were also chosen for analgesic activity test. The results of analgesic activity tests, which was performed by WRITHING Method, indicate that; the compounds with no substituents at the first position of indole ring (S_1, S_2) have better activity than the other series of compounds (S_{2a}, S_{a2}, S_{2b}, S_{b2}) when they were compared with Indomethacin. It was also determined that the methyl halide salts of synthetized compounds were less active than the HCl salts.

For the last word, it can be said that; the synthetized compounds are important and promising for the future with their analgesic and antispasmodic activities.

DETECTION OF NITRIC OXIDE SYNTHETIZING ABILITY OF MACROPHAGES FROM HEALTHY AND *Mycobacterium tuberculosis* INFECTED PEOPLE BY USING BIOASSAY METHOD

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In the present investigations, it was aimed that (1) indirect measurement of NO production by human cultured monocytes / macrophages stimulated with LPS by using two independent methods: a colorimetric measurement of the reaction of NO with Griess reagent and a bioassay for NO-mediated relaxation of preconstricted rings of guinea pig aorta; (2) to compare the nitrite amounts by the above mentioned methods and (3) to compare the ability of macrophage NO synthesis from healthy and active pulmonary tuberculous patients.

In the diazotization studies it was concluded that (1) nitrite production can be observed up to four days for obtaining significant levels of nitrite; (2) LPS (25ng/200 µl)-induced cell stimulation caused significant levels of nitrite; (3) nitrite concentrations in the culture supernatants gradually reached the peak levels at designated days following then to decrease; (4) nitrite production was reached a maximum at different time-points suggesting that this production was heterogeneous from donor to donor; (5) human monocytes can be classified into two different populations : a low nitrite-producing (<10M) and a high nitrite-producing (>10M) one; (6) in the tuberculous donors, nitrite production was observed but this production was lower than the healthy donors and (7) L-NAME decreased the NO production by macrophages isolated from healthy and tuberculous donors.

In the bioassay studies it was concluded that (8) norepinephrine preconstricted deendothelised guinea - pig aorta ring can be used for the determination of nitrite-like substances released from monocyte / macrophages; (9) these substances seems likely to be responsible for the relaxations obtained with supernatants; (10) the reason of the increased nitrite levels obtained from tuberculous patients is that the supernatants have nitrite like-activity and/or a nitrite - like relaxing activity induced by other substances both elaborate relaxation with a masked effect on vasoactive substances being found at the same time.

As a result, substances having nitrite and/or nitrite-like relaxant activity obtained from cultured human monocyte / macrophages are detectable by the diazotization and the bioassay methods but the latter method is more sensitive than the diazotization method. In measuring the NO production sensitivity of the bioassay method can be specified by using inhibitors of nitrite-like relaxing factors during culture period and/or in the organ bath.