Pharmaceutical Study on Design and Evaluation of Some Controlled Release Drug Delivery Systems

Thesis presented by
Mariza Fouad Farag Boughdady


Under Supervision of

Prof. Prof.

Hassan Mohamed ELSabbagh, Osama Abd EL-Azeem Soliman,
Ph. D. Ph. D.

Professor of Pharmaceutics, Faculty of Pharmacy, Mansoura University
Professor and head of the department of Pharmaceutics, Faculty of Pharmacy, Mansoura University

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Abstract

The goal of any drug delivery system, is to provide a therapeutic amount of a drug to a proper site in the body so that the desired drug concentration can be achieved promptly and then maintained. In recent years, considerable attention has been paid to the development of new drug delivery systems. The controlled drug delivery systems are the dosage forms which are developed to achieve the intention of better patient compliance, modified drug release, delivery of drug at the site of action, more efficient administration of drugs by various routes and hence better therapeutic effect. The aim of this investigation was to study two different controlled release drug delivery systems which are: floating drug delivery system, and niosomes as a vesicular drug delivery system.

The main objectives in this investigation were; firstly: to design gastroretentive floating tablets containing hydrochlorothiazide (HCTZ), which is widely used as diuretic for the treatment of hypertension, using different polymers. Studying of different factors affecting the floating behavior of the prepared tablets was of our goals and important target in this part. Secondly: to prepare and evaluate niosomal
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formulations containing aceclofenac (ACF), a non steroidal anti-inflammatory drug, for skin delivery.

To fulfill these goals, this thesis comprises the following two parts:

The first part deals with formulation, preparation and evaluation of hydrochlorothiazide floating tablets.

The second part deals with formulation, preparation and assessment of aceclofenac niosomes for transdermal delivery.

PART I

Formulation, Preparation and Evaluation of Hydrochlorothiazide Floating Tablets

The aim of work, in this part, was to formulate floating tablets containing HCTZ. The effects of different formulation variables on the floating behavior, tablet characteristics, as well as, the in-vitro drug release pattern from the prepared tablets were also considered. In addition, tracing of the prepared floating tablets in GIT using X ray, was a matter of interest to be evaluated in such investigation, in order to determine the exact tablet position in the GIT after oral administration. Thus, this part includes the following two chapters:
Chapter I

Formulation, Preparation and *In-vitro* Evaluation of Hydrochlorothiazide Floating Tablets

This chapter dealt with the preparation of HCTZ floating tablets using different polymers, either alone or in blends in different ratios, namely: hydroxypropyl methylcellulose (HPMC), carbopol 934 (CP 934), and sodium alginate. Polymers were used alone, or in blends of either HPMC and CP 934, or HPMC and sodium alginate, in different ratios, in the preparation of HCTZ floating tablets. The floating behavior of the prepared tablets was studied through the determination of floating lag time (FLT) for the different tablet batches. Effects of tablet hardness, and type of gas forming agent (through using either sodium bicarbonate, or light magnesium carbonate, or heavy magnesium carbonate) on the floating behavior of the prepared tablets were studied. The effect of filler type, through using either lactose monohydrate or microcrystalline cellulose (MCC), on the floating behavior of the prepared tablets was also studied. The prepared HCTZ floating tablets were also evaluated for their drug content uniformity, friability, hardness and *in-vitro* release characteristics. The results of the release study were analyzed using different kinetic orders and mathematical models.
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The obtained results revealed that:

- All the prepared tablets remained buoyant on the surface of dissolution medium for more than 12 hr, except batch H1 (prepared using 5% w/w HPMC), which underwent prompt disintegration, and batches HC2, and HC3, which were prepared using a blend of HPMC and CP 934P.

- All the batches of tablets, prepared using sodium bicarbonate as gas generating agent, were found to exhibit short FLT.

- Magnesium carbonate showed lower efficiency, as a gas-forming agent than sodium bicarbonate. A comparatively higher FLT was noticed for tablets prepared with light and heavy magnesium carbonate (19.7 min. and 51 min., respectively).

- Increasing the concentration of HPMC was found to decrease the FLT of the prepared tablets.

- Tablets prepared with low hardness value floated immediately, while those with increasing the hardness resulted in an increase in the buoyancy lag-time.

- Carbopol appeared to have a negative effect on the floating behavior.

- For tablets prepared with blend of HPMC and sodium alginate, it was found that, upon increasing the content of HPMC, and
decreasing sodium alginate, an increase in the corresponding FLT was observed.

- Tablets prepared with MCC showed higher FLT than those prepared with lactose monohydrate.
- Increasing the concentration of HPMC was found to reduce the drug release rate.
- Tablets with low hardness showed faster drug release compared with those having higher hardness value.
- Incorporation of CP 934 with HPMC K4M was found to decrease the release of HCTZ.
- Increasing the amount of alginate incorporated in the tablet matrices led to increasing retardation of drug release.
- Sodium bicarbonate acted as a pH modifier for tablets prepared using sodium alginate polymer, and consequently minimizing matrix lamination, and hence more retardation of drug release was obtained.
- High dissolution rate was observed with sodium alginate than that obtained with HPMC, due to the low swellability of the former.
- On the other hand, no significant difference was noticed in the in vitro release behavior between both batches ML and MH
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(prepared with light and heavy magnesium carbonate, respectively).

Also, no significant difference was found between both batches H4 and H4b (prepared with lactose monohydrate and MCC, respectively), regarding the *in vitro* release behavior.

Chapter II

**Evaluation of the Intragastric Floating Behavior of Prepared Tablets Using X-ray Radiography**

This chapter dealt with the *in vivo* evaluation of the intragastric floating behavior of prepared tablets using X-ray radiography. Thus, the optimum formula that combined excellent properties as regards to floating behavior, sustained drug release characteristics and good physical characters was chosen for this study. This *in vivo* investigation was carried out in healthy human volunteers, to determine the gastric retention time (GRT). Placebo tablets of batch H4 were prepared, with the incorporation of BaSO$_4$, to make the tablets X-ray opaque. The tablet administration was performed in the fasting state, as well as the fed state. Radiographic imaging was done in the abdominal region, at hourly intervals, to visualize the exact location of the tablet position in GIT. The obtained results revealed that:
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The *in vitro* FLT of the barium sulfate-loaded tablets was increased compared with the original formula, due to the high relative density of barium sulfate.

A gastric floating tablet administered in the fasted state could be removed within as little as 1–2 hr, due to strong contractile activity which occurs under fasting conditions.

Gastric residence time of the prepared tablets was found to be 180 min., in the fed state.

Gastric residence time can be significantly increased under the fed conditions since the MMC is delayed.

PART II

Formulation, Preparation and Assessment of Aceclofenac Niosomes for Transdermal Delivery

The work in this part concerned with studying the formulation of niosomes containing ACF followed by evaluating the parameters viz; entrapment efficiency (EE %), particle size, shape, and *in vitro* drug release. In addition, Incorporation of the best niosomal formulation into different polymer gels and transdermal patches was done. Their *in vitro* drug release pattern and *in vivo* behavior were also aimed to be investigated. This part includes the following two chapters:
Chapter I  
Formulation, Preparation and Evaluation of Aceclofenac Niosomal Formulations

The objective of this chapter was to formulate ACF in niosomal formulations, with non ionic surfactant (span 60) and cholesterol (CH) in different molar ratios, and to characterize the prepared niosomal formulations with respect to their morphology, EE % and in vitro drug release behavior. This was achieved through the preparation of different niosomal formulations, using Span 60 and CH in different molar ratios, viz., 7.5: 2.5 (N1), 6: 4 (N2), and 5: 5 (N3). The characterization of the prepared formulations was performed through the determination of EE %. The niosomal formulations were also subjected to scanning electron microscopy (SEM), transmission electron microscopy (TEM) and differential scanning calorimetry (DSC). The in vitro release of ACF from niosomes was also investigated. The best formulation, as regards the tested characteristics, was incorporated into different gel bases [CP 934 (1% w/w), sodium carboxy methyl cellulose (SCMC) (3% w/w), and HPMC (2% w/w)], and transdermal patches for making sustained therapeutic action.
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From the obtained results, it was evident that:

- Maximum entrapment of drug (46.5% ± 3.75) was obtained when Span 60 and CH were used in the ratio of 6:4 (formulation N2).
- Incorporation of CH into niosomes was found to increase the EE% of ACF up to an optimum concentration of CH (span: CH of molar ratio 6:4), while further increase in CH content, led to reduction in EE%.
- Entrapment efficiency was increased, from 26.6% ± 2.87 to 46.5% ± 3.75, as the drug concentration was increased from 30 to 50 mg, respectively.
- Scanning electron microscopy demonstrated that, the vesicles are well identified, and are present in a nearly perfect sphere-like shape.
- Smaller particle size of niosomes was obtained with increasing the CH molar ratio.
- The DSC study confirmed the formation of vesicles of niosomes.
- Incorporation of ACF in all niosomal formulations was associated with slower release profiles than the free drug.
- The increase in CH molar ratio from (span 60: CH 7.5:2.5) in formulation (N1) to (span 60: CH 6:4) in formulation (N2)
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markedly reduced the efflux of the drug, during the in vitro drug release.

- Further increase in CH molar ratio from (span 60: CH 6:4) (formulation N2) to (span 60: CH 5:5) (formulation N3) was accompanied by faster drug release.

- Drug release kinetics from the different prepared niosomal formulations were found to follow Higuchi model.

- Carbopol niosomal gel provided a more retarded drug release than free drug gel, with a release percent of 22.3 ± 0.76% and 35.97 ± 1.32% for CN and CA gel formulations after 6 hr, respectively.

- Sodium carboxy methyl cellulose based gel containing the niosomal formulation (SN) has significantly retarded drug release than its corresponding niosomal formulation (N2) without SCMC, having a percent drug release of ACF after 6 hr of 30.2 ± 0.74% and 53.8 ± 7% for SN gel and N2 niosomal formulation, respectively.

- A retardation of ACF release was observed in the case of HPMC niosomal gel (HN) than the niosomal formulation N2, without HPMC. The percent drug release of ACF after 6 hr was found to be 36.6 ± 0.79% and 53.8 ± 7% for HN gel and N2 niosomal formulation, respectively.
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Hydroxypropyl methylcellulose gel containing the free drug (Hₐ) showed faster drug release than Hₙ and N₂, where the percent of drug release after 6 hr was 73.4 ± 0.82%, for Hₐ.

Incorporation of niosomes in gels, led to slower drug release than the corresponding niosomal formulation itself, without gels. All the prepared gels followed Higuchi matrix, except for Hₐ gel which followed the first order kinetic model.

Patch Pₕ prepared using niosomal formulation N₂ showed a slower drug release than patch Pₜ prepared with the free drug. The percent drug release was found to be 34.13 ± 6.48 % and 62.01 ± 4.76 % for transdermal patches Pₕ and Pₜ, respectively.

The release data of both transdermal patches (Pₕ and Pₜ) were found to be best fitted to zero order kinetic model.

Chapter II

In vivo Study on the Anti-inflammatory Activity of Aceclofenac Niosomal Formulations

In this chapter, the objective of the investigation was to encapsulate ACF in niosomes and incorporate the prepared niosomes into suitable dermal base, to improve the therapeutic index and patient compliance. The anti-inflammatory action of the optimized
formulation N2 after incorporation in 2% w/w HPMC gel base, was evaluated by the carrageenan-induced hind paw edema method. The experiment depends on measuring the paw thickness prior to injection of carrageenan and thereafter at hourly intervals. Edema is expressed as the increase in paw thickness after carrageenan injection relative to the pre-injection value for each animal. The preparation containing the anti-inflammatory drug is applied either before (protective application) or after carrageenan injection (treatment application).

From the obtained results, it was evident that:

- Aceclofenac formulations showed a significant percentage inhibition of edema compared with the control at all time intervals, during the protective and the treatment application procedures.
- The difference in edema rate, and edema inhibition percentage; either between the niosomal gel (G_N) and the free drug gel (G_A), or between the niosomal gel and the marketed product was insignificant, at all the time intervals up to six hrs, during the protective application procedure.
- During the protective application procedure, niosomal gel (G_N) showed a significant increase in percent edema inhibition, when compared with the free drug gel (G_A), with percent edema inhibition values of 65.2 % and 55%, respectively, after 24 hr.
Also, a significant difference was observed between the niosomal gel and the marketed product, which showed percent edema inhibition values of 65.2% and 56%, respectively, after 24 hr, in the protective application procedure.

During the treatment application procedure, niosomal gel (GN) showed a significant increase in percent edema inhibition value (28.9%) after 6 hr, when compared with the standard group, which showed a value of 16.6%. Niosomal gel (GN) exhibited also a significant higher anti-inflammatory activity compared with the free drug gel (GA) after 6 hr, which having percent edema inhibition values of 28.9% and 18.2%, respectively.

A further significant increase in the edema inhibition percent of the niosomal gel to 58.4%, at the end of 24 hr was found, compared with 38.3 and 38.2% for the standard and free drug gel (GA) groups, respectively.

The application of niosomal gel produced a significant reduction of rat paw edema, compared with the free drug gel and marketed product, after 24 hr, indicating a better skin permeation, due to accumulating capacity and deposition of ACF from niosomes.

The results of this study demonstrated that, niosomal gel formulations possess great potential for prolonging ACF release,
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and considered a promising topical formulation for effective therapy, which was ascribed to better anti-inflammatory activity than commercial cream.

Also, the results indicate that the niosomes can be used as a novel drug delivery carrier for skin targeting of ACF for its sustained anti-inflammatory action.