APPLICATION OF THE NEW OROSLIPPERY TECHNOLOGY IN THE PREPARATION OF ENTERIC SLIPPERY COATED TABLET OF NAPROXEN

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INTRODUCTION

Dysphagia or swallowing difficulties is a common problem in tablet dosage form affecting about 50% of the population [1], representing the major limitation of the most commonly used tablets [2, 3]. For this reason, many patients do not take their medications as prescribed, which results in a high incidence of noncompliance and ineffective therapy [4]. Consequently, different tablet dosage forms were developed to overcome swallowing difficulties, in which drugs are administered orally without the need for chewing or prior dispersion or dissolution in water in order to produce a systemic effect [5]. Recently, a new tablet dosage form oroslippery tablet (OSTs) was developed in our previous publication to overcome dysphagia and to alleviate some disadvantages of the traditional tablet, through hydrating it in the oral cavity and offering easily slipperiness of the intact tablet with good taste masking effect in the mouth without the need of water [6]. Naproxen is a propionic acid derivative. It belongs to a group of non-steroidal anti-inflammatory drugs (NSAIDs) that have analgesic, anti-inflammatory and antipyretic properties, through inhibiting the enzyme cyclo-oxygenase (COX-1) that might causes GIT irritation [7]. Enteric-coated tablets were designed to pass unchanged through the stomach to the intestine where they disintegrate to allow drug dissolution and absorption to give its therapeutic effect and widely employed when the drug is irritating the gastric mucosa [8]. This work is a developed application of new easily swallowed oroslippery enteric coated tablet for naproxen with good taste masking property that may be used as an alternative to conventional uncoated naproxen tablet.

MATERIALS AND METHODS

Materials

Naproxen, croscarmellose sodium (CCS), sodium saccharin, polyethylene glycol 6000 (PEG 6000) and eudragit L-100 (eud.) (Samara drug industry, Iraq). Mannitol and magnesium stearate (Mg stearate) (Provizer pharma, India). Crospovidone (CP) (Aladdin chemistry, China). Xanthan gum (xan.), peppermint oil, red iron oxide, talc and titanium dioxide (Himedia, India). All other chemicals, solutions and reagents used were of analytical grade.

Methods

Preparation of naproxen core tablets

Naproxen core tablets were formulated by direct compression using 11 mm punch and die set, using the ingredients in (table 1). The pre-weighed amounts of all excipients (except Mg stearate) were mixed together for about 10 min, followed by additional 5 min mixing after addition of Mg stearate [9]. These core tablets were prepared using three different concentrations of CCS (2%, 4% and 6%) to demonstrate their effect on the disintegration and release of naproxen from the prepared tablets.

Table 1: Composition of the prepared naproxen core tablets

| Ingredients     | C1    | C2    | C3    |
|-----------------|-------|-------|-------|
| Naproxen        | 250   | 250   | 250   |
| CCS             | 8     | 16    | 24    |
| Mannitol        | 130   | 130   | 122   |
| Mg stearate     | 4     | 4     | 4     |
| Total weight    | 400   | 400   | 400   |

All quantities are expressed in mg.
Preparation of the enteric slippery coat

Three different enteric slippery coating formulas (table 2) were prepared. This is achieved by the following steps:

1st step: preparation of the enteric polymer solution

Eudragit L-100 (eud.) (Enteric polymer) was added gradually in three different concentrations (13.5%, 15.5% and 17.5%) to a distilled water containing 1N sodium hydroxide (NaOH) and mixed together at room temperature using magnetic stirrer at 1000 rpm for about 10 min until a lump free solution obtained.

2nd step: preparation of the pigment dispersion

This was prepared by dissolving sodium saccharin (as sweetening agent) in distilled water then followed by the addition of PEG 6000 (as plasticizer) and mixing for about 10 min in magnetic stirrer at 1400 rpm at room temperature, after that the pigment (red iron oxide), the opacifier (titanium dioxide) and the anti-adherent (talc) were added and mixed for another 10 min.

3rd step: preparation of the xanthan gum mixture

Xanthan gum (xan.) as slipperiness inducing agent [10, 11], was added to the previously heated distilled water (39 °C) and homogenized using magnetic stirrer at 600 rpm for about 5 min.

4th step: preparation of the enteric slippery coating

The final slippery enteric coating was prepared by adding the filtered pigment dispersion to the enteric polymer solution and mixing for about 10 min at 400 rpm, followed by its addition onto the xanthan gum mixture along with the peppermint oil (flavouring agent) which further homogenized for 10 min at 400 rpm at room temperature.

| Ingredients             | T1          | T2          | T3          |
|-------------------------|-------------|-------------|-------------|
| Eud.                    | 13.5%       | 15.5%       | 17.5%       |
| 1N NaOH                 | 4%          | 4%          | 4%          |
| Red iron oxide          | 1%          | 1%          | 1%          |
| Titanium dioxide        | 2%          | 2%          | 2%          |
| Tak                     | 2%          | 2%          | 2%          |
| Xan.                    | 0.3%        | 0.3%        | 0.3%        |
| Sodium Saccharin        | 2.5%        | 2.5%        | 2.5%        |
| Peppermint oil          | 0.5%        | 0.5%        | 0.5%        |
| PEG 6000                | 10%         | 10%         | 10%         |
| Distilled water         | Up to 100 ml| Up to 100 ml| Up to 100 ml|

Preparation of naproxen enteric-coated oroslippery tablets

Eight different enteric coated OSTs of naproxen were prepared (table 3) by dipping the core tablet (C1) in each of the enteric slippery coating solutions (T1, T2 or T3) once referred as (C1,T1, C1,T2 and C1,T3), in the enteric coating solution (T1), and double referred as (C1,T1,T2, C1,T1,T3 and C1,T2,T3) in formulas (F1-F6) to study the effect of eudragit concentration and coating level. The best eudragit concentration and coating level where used (F1-F6) to study the effect of eudragit concentration and coating level. The best eudragit concentration and coating level where used (F1-F6).

| Naproxen enteric coated OSTs | Composition |
|-----------------------------|-------------|
| F1                          | C1,T1       |
| F2                          | C1,T2       |
| F3                          | C1,T3       |
| F4                          | C1,T2,T3    |
| F5                          | C1,T1,T1    |
| F6                          | C1,T1,T3    |
| F7                          | C1,T2,T2    |
| F8                          | C1,T1,T2    |

Pre-compressibility evaluation for the core tablet powder

The flowability of the core tablet powder was evaluated by measuring carr’s or compressibility index. Hausner’s ratio and angle of repose. The first two parameters were evaluated by the calculation of the bulk and tap densities [12, 13], while the latter was measured by the fixed base method [3].

Post-compressibility evaluation

Physical properties

The physical properties of the prepared core and coated tablets were evaluated, where the weight variation and friability were studied according to the USP requirements, while the hardness and thickness were estimated using electrical hardness tester and vernier caliper respectively [14-16].

Disintegration test

This test was performed (according to the USP specification) for the enteric coated slippery tablet in 0.1 N HCl for 2 h, where no sign of disintegration should be observed then followed in phosphate buffer pH 6.8 and record the time for complete disintegration [12, 17].

Dissolution test

Drug release profile for the enteric coated oroslippery tablets was evaluated in vitro using dissolution apparatus type II. According to the USP the dissolution test was performed at 37 °C where the percent drug release should not exceed 10% of the labeled amount after 2 h in 0.1 N HCl and not be less than 80% after 45 min in phosphate buffer pH 6.8 [12, 18, 19].

Five milliliter samples were withdrawn each time and analyzed by UV-visible spectrophotometer at wave length of 350 nm. The test was done in triplicate and the average value was compared by using the percent drug released in 2 h (%D) and the time required to reach 80% release (T80).

Variables affecting drug release

The following variables were studied to optimize the enteric coated slippery tablets:
Effect of eudragit L-100 concentration

Formulas F1, F3, F5 (mono-coated) and formulas F2, F4, F6 (double-coated) were prepared using different concentration of eud. (13.5%, 15.5% and 17.5% w/w) respectively to demonstrate its effect on the release of naproxen from the prepared tablets.

Effect of coating level

The effect of coating layer was shown in formulas (F1-F6) were mono and double coating level was performed using TpTp coating solution on C core tablet to see its effect on the release of naproxen from the prepared tablets.

Effect of superdisintegrant concentration

The effect of CCS concentration on drug release from the prepared tablets was studied using (F6-F8) containing 8, 16 and 24 mg CCS respectively.

Content uniformity test

The optimum formula F8 (CfTf) was subjected to content uniformity test, by crushing a randomly selected 10 tablets individually and dissolving them in methanol, the solution was filtered and assayed for naproxen content using UV-visible spectrophotometer at wave length of 330 nm [20].

Drug excipient compatibility test

The pure drug (naproxen) powder, core tablet (C) and enteric coated oroslippery tablets (F1-F8) were subjected to drug-excipient compatibility test by using the pressed-disk technique [21] in order to detect any physicochemical incompatibilities between the drug and different excipients.

Statistical analysis test

The results were expressed as mean±standard deviation, and were analysed using analysis of variance (ANOVA) single factor to compare the sample means and to determine the statistical significance, at which (P<0.05) was considered to be significant.

RESULTS AND DISCUSSION

Pre-compressibility and post-compressibility studies for the prepared core tablets and enteric-coated oroslippery tablets

Table 4 illustrates all pre-recompression parameters including angle of repose, Carr’s index and Hausner ratio for the prepared core powder mixture (C:C) for each formula, and its corresponding type of flow. These results clearly demonstrated that all core tablets possessed an acceptable flow ability according to USP.

Table 4: Pre-compressibility results for the prepared core tablets

| Formula | Angle of repose (degree) | Carr’s index | Hausner ratio | Type of flow |
|---------|--------------------------|--------------|---------------|--------------|
| C1      | 32.2±1.30                | 12.79±2.25   | 1.17±0.05     | Good         |
| C2      | 31.7±2.27                | 11.75±2.05   | 1.14±0.16     | Good         |
| C3      | 29.14±1.05               | 9.33±0.54    | 1.11±0.50     | Excellent    |

(All results are expressed as mean±SD, n=3)

In addition physical properties for the formulated core (C:C) and enteric coated oroslippery tablets (F1-F8) were showed in (table 5 and 6) respectively. The results clearly demonstrated non-significant differences in the physical properties between the prepared core tablets (C1, C2, and C3). A significant improvement in the friability was observed after coating comparing to the core tablets, while non-significant reduction in the friability was observed between formulas F1, F3 and F5 (monolayer coat) in comparison to F2, F4, F6 (double layer coat) respectively that could be explained by the significant increase in the coated tablets weight with a non-significant increment in coat thickness after the application of double coat. Also, a non-significant increase in the coated tablet weight and thickness was detected between the mono coated formulas themselves (F1, F3, and F5) and also between the double coated formulas themselves (F2, F4, and F6) where different coating solution TpTp and Tf used. This was attributed to the slight increase in the viscosity of the enteric coating formulas resulting from increasing eudragit L-100 concentration from 13.5% in (F1, F2) to 15.5% and 17.5% in (F3, F4) and (F5, F6) respectively, an effect which might increase the hydrodynamic drag during the dipping process [22-24]. Furthermore, non-significant differences were observed in the hardness between the core and coated tablets and between the coated tablets themselves indicating that the enteric oroslippery coating formula had a negligible effect on the hardness.

Table 5: Physical properties for the formulated core tablets

| Formula | Friability (%) | Hardness (kg/cm²) | Thickness (mm) | Weight variation (mg) |
|---------|---------------|-------------------|----------------|--------------------|
| C1      | 0.6±0.01      | 5.23±1.03         | 5.42±1.34      | 390±1.56           |
| C2      | 0.72±0.03     | 5.67±1.21         | 5.44±1.02      | 399±1.89           |
| C3      | 0.66±0.05     | 5.96±1.66         | 5.43±1.33      | 397±2.02           |

(Results are expressed as mean±SD, n=3)

Table 6: Physical properties for the enteric coated oroslippery tablets

| Formula | Friability (%) | Hardness (kg/cm²) | Thickness (mm) | Weight variation (mg) |
|---------|---------------|-------------------|----------------|--------------------|
| F1      | 0.29±0.01     | 5.73±1.10         | 5.51±1.04      | 436±1.56           |
| F2      | 0.21±0.03     | 5.43±1.01         | 5.63±0.11      | 454±2.13           |
| F3      | 0.25±0.02     | 5.65±1.03         | 5.54±1.22      | 437±1.06           |
| F4      | 0.20±0.01     | 5.93±1.00         | 5.66±1.23      | 455±2.35           |
| F5      | 0.18±0.02     | 5.21±0.91         | 5.57±1.06      | 438±2.45           |
| F6      | 0.14±0.01     | 5.54±0.23         | 5.68±1.53      | 456±1.08           |
| F7      | 0.13±0.02     | 5.89±1.23         | 5.67±1.09      | 457±2.33           |
| F8      | 0.15±0.02     | 5.36±1.01         | 5.69±1.03      | 456±1.56           |

(Results are expressed as mean±SD, n=3)
In vitro disintegration test for the prepared enteric-coated oroslippery tablets

The results of In vitro disintegration of the prepared tablets were showed in (table 7). These results clearly demonstrate that after increasing eudragit L-100 amount by either the application of higher concentration of eud. or the application of double coating the formulas F1-F5 fails to pass the USP requirement of disintegration with the exception of F6 that remains intact for 2 h in 0.1 N HCl but require a long time to disintegrate (120 min) in phosphate buffer pH 6.8. While a significant reduction in disintegration time in phosphate buffer was observed in formulas F7 and F8 were comparing with F6 due to the application of higher concentration of CCS in naproxen core tablets but with suitable protection from disintegration in acidic media and F8 gave the best result.

Table 7: In vitro disintegration time for the prepared naproxen enteric-coated oroslippery tablets

| Formula | DT in min (in 0.1 N HCl) | DT in min (in phosphate buffer pH 6.8) |
|---------|-------------------------|---------------------------------------|
| F1      | [-]                     | [-]                                   |
| F2      | [-]                     | [-]                                   |
| F3      | [-]                     | [-]                                   |
| F4      | [-]                     | [-]                                   |
| F5      | [-]                     | [-]                                   |
| F6      | intact tablet for 2 h   | 120±1.09                              |
| F7      | intact tablet for 2 h   | 17±0.76                               |
| F8      | intact tablet for 2 h   | 8±1.36                                |

(Results are expressed as mean±SD, n=3), *where (‘-) denotes to the beginning of disintegration in 0.1 N HCl

Table 8: In vitro release data for the prepared naproxen enteric-coated oroslippery tablets

| Formula | % D_{2h}  | T_{80%}(min) |
|---------|-----------|--------------|
| F1      | 20.09±0.56 | More than 165 |
| F2      | 12.42±1.78 | More than 165 |
| F3      | 13.68±2.76 | More than 165 |
| F4      | 10.54±1.09 | More than 165 |
| F5      | 2.45±2.96  | More than 165 |
| F6      | 0          | More than 165 |
| F7      | 0          | 165±2.71      |
| F8      | 0          | 140±1.05      |

(Results are expressed as mean±Standard deviation, n=3)

Fig. 1: Effect of eudragit L-100 concentration on the release of naproxen from monolayer enteric-coated oroslippery tablets (F1, F3, F5) in (0.1N HCl) for 2 h followed by their addition to (phosphate buffer pH 6.8) for 45 min, where all core tablets containing 2% CCS as super disintegrant (Error bars indicate mean±SD, n=3)

Fig. 2: Effect of eudragit L-100 concentration on the release of naproxen from double layer enteric-coated oroslippery tablets (F2, F4, F6) in (0.1N HCl) for 2 h followed by their addition to (phosphate buffer pH 6.8) for 45 min, where all core tablets containing 2% CCS as super disintegrant (Error bars indicate mean±SD, n=3)
Variables affecting drug release

Effect of eudragit L-100 concentration

Results of *in vitro* release of naproxen from the enteric-coated OSTs are summarised in (table 8) and (fig. 1 and 2). Formulas from F1-F6 were formulated to show the effect of different concentrations of eudragit L-100 after application of mono-coating in (F1, F3, and F5) and double coating in (F2, F4, and F6) using the same core tablet containing 2% CCS. Increasing the concentration of eudragit L-100 from 13.5% in F1 and F2 to 15.5% in F3 and F4 and finally to 17.5% in F5 and F6, that were respectively mono and double coated with the enteric coating dispersion; causes a significant reduction in % D_{2h} in 0.1 N HCl and hence significantly increasing the acid resistance of the enteric coating due to the higher amount of eudragit L-100 [14], although all of these formulas fail to meet the requirement of USP in that they released more than 10% of the labeled amount in 2 h (Except F6) and all of them required more than 45 min in phosphate buffer pH 6.8 to reach 80% release.

Effect of coating level

Results in (fig. 3-5) clearly demonstrate the effect of coating level on naproxen release from the prepared tablets. Increasing coating level in each eud. Concentration from mono coating to double coating in (F1, F2), (F3, F4) and in (F5, F6) causes a significant reduction in the dissolution process represented by a significant reduction in % D_{2h} in Formulas F1-F6. The best acid resistance in F6 where 0% drug release after 2 h, although all these formulas (F1-F6) required more than 45 min in phosphate buffer pH 6.8 to reach 80% [12].

![Fig. 3: Effect of coating level (with 13.5% eud.) on the release of naproxen from enteric-coated oroslippery tablets (F1 and F2) in (0.1N HCl) for 2 h followed by their addition to (phosphate buffer pH 6.8) for 45 min, where all core tablets containing 2% CCS as super disintegrant (Error bars indicate mean±SD, n=3)](image)

![Fig. 4: Effect of coating level (with 15.5% eud.) on the release of naproxen from enteric-coated oroslippery tablets (F3 and F4) in (0.1N HCl) for 2 h followed by their addition to (phosphate buffer pH 6.8) for 45 min, where all core tablets containing 2% CCS as super disintegrant (Error bars indicate mean±SD, n=3)](image)

![Fig. 5: Effect of coating level (with 17.5% eud.) on the release of naproxen from enteric-coated oroslippery tablets (F5 and F6) in (0.1N HCl) for 2 h followed by their addition to (phosphate buffer pH 6.8) for 45 min, where all core tablets containing 2% CCS as super disintegrant (Error bars indicate mean±SD, n=3)](image)

Effect of superdisintergrant concentration

The previous data clearly illustrated that all formulas (F1-F6) failed to pass the USP requirement for disintegration and release, with the exception of F6 which remains intact in acidic media but required a long time to disintegrate (120 min) in phosphate buffer pH 6.8. Therefore, Formulas F7 and F8 were prepared using cores containing 2% and 4% of CCS as superdisintergrant.

The results in (fig. 6) demonstrated a significant acid resistance after 2 h in 0.1 N HCl followed by a significant reduction in DT and T_{80%} in phosphate buffer pH 6.8 resulting from the effect of CCS as a superdisintergrant which led to fast burst release of naproxen tablet once it is introduced in intestine [17]. For this reason F8 was selected as the optimum formula since it gave the best acid resistance with fast and high % drug release in phosphate buffer pH 6.8.
Content uniformity

The optimum naproxen enteric coated OSTs (F8) was complied with USP specification, as no tablet of the randomly selected ten tablets was outside the range (85-115%), indicating the uniform distribution of naproxen in the prepared tablets.

Drug excipient compatibility

The FTIR spectrum of pure naproxen as showed in (fig. 7A) in addition to the selected core (C1) together with the enteric coated OSTs represented (F8) as showed in (fig. 7B) has the same characteristic absorption bands of pure naproxen at the C=O stretching region, which are between (1600 and 1800) cm\(^{-1}\)[20], indicating that no interaction occurred between the drug and other components of the prepared OSTs.

CONCLUSION

In this study, preparation of enteric slippery coated tablets for naproxen showed that it can be readily swallowed (avoiding problems usually associated with tablet dosage forms). An improvement and high stability in disintegration or release properties were achieved after application of this new technology. It was successful to show that enteric oroslippery tablets for naproxen didn’t dissolve or disintegrate in the stomach, but gave fast 100% release once it reaches to the intestine. Therefore, it can be concluded that application of a slippery coating technology in the preparation of enteric coated tablet for naproxen was a creative and has a great potential to be an effective approach for new delivery of drugs.

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CONFLICT OF INTERESTS

Declared none

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Fig. 6: Effect of different CCS concentration on the release of naproxen from enteric-coated oroslippery tablets in (0.1N HCl) for 2 h followed by their addition to (PH 6.8 phosphate buffer) for 45 min, where all formulas are double coated with 17.5% eudragitL-100 (Error bars indicate mean±SD, n=3)

Fig. 7: FTIR spectrum of (A) naproxen and (B) F8
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