Enteral Coated Capsules for Extended Release of Lansoprazolemucoadhesive Multiple-Unit Mini Patches

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ABSTRACT

The current study aims to the preparation and assessment of novel oral mucoadhesive multiple-unit mini patches (MMMP) of lansoprazole (LAN) for extended-release. MMMP of LAN in enteric-coated capsules were prepared and evaluated using chitosan in combination with xanthan gum, guar gum, tragacanth or acacia in the ratios of 19:1, 9:1, 4:1, 1.5:1 and 0.66:1 employing 2% acetic acid as a solvent for chitosan, purified water as a solvent for natural gum polymers and glycerin 0.12 mL as a plasticizer. The prepared films (0.5 mm dia) were filled into hard gelatin capsules which were enteric-coated. The prepared MMMP were characterized for surface texture, thickness, folding endurance, moisture content, moisture uptake, mucoadhesive strength, drug content uniformity, In vitro drug release and accelerated stability studies. The SEM photographs showed the rough to smooth pattern of surfaces of patches. The thickness of MMMP found between 43.62±0.27 and 49.53±0.11 mm; mean weight was between 13.81±0.14 and 14.94±0.15 mg; a percentage of swelling was between 215±5.39 and 473±6.72; moisture content was between 1.04±0.06 and 2.67±0.24; mucoadhesion was found between 5.5±0.2 and 12.3±0.6 h and the drug content was found between 95.08±3.42% and 99.16±4.73% for all formulations.

INTRODUCTION

Intestinal patches mostly millimeter sized gives An interesting stage to oral conveyance for pills which have poor oral bioavailability, requiring their organization by injections. They would propelled toward transdermal patches, which despite comparable theoretical design; work in extremely different physiological environments (Banerjee and Mitragotri, 2017). A few gastrointestinal patavium frameworks give bio adhesion, medication regardless of security starting with acidic nature’s domain Also unidirectional release (Tao and Desai, 2005; Kirsch et al., 2017; Teutonico and Ponchel, 2011). On addition, these units make An secondary centralization gradient to pill transport, which encourage uptake of stacked proteins through the intestinal membrane (Gupta et al., 2013). Consequently, intestinal patch- built units would constantly create to oral conveyance from claiming a few pills,
for example, insulin (Banerjee et al., 2017) evendode, calcitonin, interferon-α, erythropoietin and human granulocyte colony-stimulating element to the medication of diabetes, osteoporosis, hepatitis or chemotherapy. A patent described pH-dependent mucoadhesive patches for unidirectional release of drugs (Rossi et al., 2000).

MATERIALS AND METHODS

Lansoprazole from Dr. Reddy’s Laboratories, Hyderabad, India; chitosan and tragacanth from Central Drug House Pvt. Ltd., Delhi, India; xanthan gum from Edict pharmaceuticals, Chennai, India; were gratis samples. Guar gum bought by S.D. Fine-Chemicals Ltd., Boisar, Mumbai, India. Acacia, glycerin, HCl, acetic acid and additional substances are bought by S.D Fine Chemicals Pvt. Ltd., Mumbai, India (Banerjee et al., 2016).

Preparation of MMMP in enteric-coated capsules for controlled release of LAN

Solvent casting technique is hired by the grounding of MMMP. The patches are arranged by melting the specified amount of chitosan in 10 mL of 2% acetic acid solution along with the selected natural polymer gum (Guar gum, Xanthan gum, Tragacanth or Acacia) in 10 mL of water (Beneke et al., 2009).

Characterization of MMMP of LAN

The MMMP were visually inspected for colour, clarity, flexibility and smoothness. The free MMMP prepared were evaluated for a physical appearance by visual observation. The thickness of the MMMP was measured by a ‘Mitutoyo (Japan) Dial Gauge’. The mean of the five observations were calculated. Calibration curves of the drug (Streubel et al., 2006).

Instrumental analysis of MMMP

FTIR spectra were recorded with FTIR spectrophotometer (Bruker Alpha, UK). Tests were readied Toward KBR circle technique (2 mg test for 200 mg KBR) and analyzed On transmission mode. Lan and readied MMMP were assessed (Iwahi et al., 1991). Those examining go might have been 400–4000 cm\(^{-1}\). The thickness was found between 43.62±6 and 346±5 number of times of folding. The flatness for all the patches was 100%. The swelling content was between 1.04±0.06 and 2.67±0.24; mucoadhesion was found between 5.5±0.2 and 12.3±0.6 h29 and the drug content was between 95.08±3.42% and 99.16±4.73% for all formulations (Table 1).

Filling of MMMP in into hard gelatin capsules

The MMMP filled capsules are enteric-coated by the method reported by Fang et al. The MMMP are filled into hard gelatin capsules were enteric-coated by HPMCAS/Eudragit L dispersion with a blend ratio of 1:3.

In vitro drug closure study

Dissolution trainings are approved by utilizing USP XXIII closure test apparatus (hamper type, Disso 2000, Lab India). Five patches of MMMP totaling 30 mg of LAN was filled in a hard gelatin capsule and enteric-coated as discussed above (Fang et al., 2014).

Stability studies of optimized MMMP

The optimized MMMP of chitosan containing various proportions of xanthan gum, guar gum, tragacanth or acacia were divided. Previously, will two gatherings. Every bunch about formulations were put independently done solidness chamber which is looked after toward 40±50C/75% rh to three months Also consistently the formulations starting with each one assembly were subjected with disintegration investigations Also % medication arrival might have been ascertained (Yan et al., 2001). Those comparability element (f2) provided for Toward SUPAC rules for An altered arrival measurement structure might have been utilized Concerning illustration a premise with think about disintegration profiles previously, then after solidness investigations in the display investigation (Murthy, 2016).

RESULTS AND DISCUSSION

An interesting advancement of mucoadhesive approach is mucoadhesive devices that delivery drugs into the small intestine. Mucoadhesive multiple-unit mini patches (MMMP) were successfully prepared using chitosan in various combinations with guar gum, xanthan gum, tragacanth oracacia (Lewis et al., 2007).

Characterization of MMMP

The SEM photographs further showed the same pattern of surfaces at 100x (Figure 1). The MMMP could be filled into capsules which were further treated with formaldehyde to attain enteric coating (E and F). The thickness was found between 43.62±0.27 and 49.53±0.11 mm for all formulations (Dharani, 2010). The folding endurance was found between 179±6 and 346±5 number of times of folding. The flatness for all the patches was 100%. The swelling was between 215±5.39 and 473±6.72%; moisture content was between 1.04±0.06 and 2.67±0.24; mucoadhesion was found between 5.5±0.2 and 12.3±0.6 h29 and the drug content was between 95.08±3.42% and 99.16±4.73% for all formulations (Table 1).

Fourier Transform Infrared (FT-IR) Spectroscopy

The results of FTIR are showed. The FTIR spectrum of pure LAN drug showed the characteristic absorption peaks of LAN appeared at 3215.96, 2982.36 & 2928.56, 1578.50, 1281.32, 1114.58 denoting
Table 1: Characterization of MMMP

| Formulati Code | Thickness (µm) | Weight of mini patch (mg) | Folding endurance (#) | % Moisture Content | Moisture Uptake (h) | Muco-adhesive Strength (%) | Drug Content (%) |
|----------------|---------------|--------------------------|----------------------|-------------------|---------------------|--------------------------|-----------------|
| FXF1           | 46.34+0.12    | 13.83+0.17               | 180+3                | 1.12+0.07         | 2.33+0.9            | 10.23+1.12              | 95.12+0.07      |
| FXF2           | 47.28+0.14    | 13.89+0.20               | 183+3                | 1.25+0.05         | 2.45+0.11           | 11.47+1.15              | 96.74+0.04      |
| FXF3           | 48.13+0.09    | 14.10+0.23               | 196+4                | 1.34+0.09         | 2.47+0.16           | 11.56+1.47              | 97.28+0.09      |
| FXF4           | 48.82+0.16    | 14.16+0.26               | 201+4                | 1.43+0.04         | 2.48+0.19           | 11.59+1.58              | 98.46+0.06      |
| FXF5           | 49.34+0.12    | 14.94+0.15               | 346+2                | 1.52+0.07         | 2.67+0.16           | 12.3+0.6               | 99.04+0.01      |
| FGF1           | 45.12+0.14    | 13.86+0.15               | 194±3                | 1.14+0.06         | 1.45±0.7            | 6.02±1.15              | 96.41±0.08      |
| FGF2           | 46.34+0.11    | 13.89+0.22               | 219±5                | 1.27+0.04         | 1.52±0.09           | 7.48±1.12              | 97.69±0.05      |
| FGF3           | 47.28+0.04    | 13.90+0.23               | 272±6                | 1.36±0.08         | 2.63±0.11           | 7.56±1.31              | 98.36±0.04      |
| FGF4           | 48.18+0.13    | 14.16+0.21               | 297±9                | 1.45+0.06         | 2.68±0.08           | 7.94±1.28              | 98.53±0.07      |
| FGF5           | 47.86+0.14    | 14.86+0.21               | 300±4                | 1.47±0.01         | 2.65±0.11           | 8.5±0.4               | 98.59±0.09      |
| LTF1           | 43.28+0.07    | 13.90+0.17               | 186±5                | 1.10±0.03         | 2.27±0.04           | 9.2±1.08               | 97.53±0.07      |
| LTF2           | 46.57+0.09    | 13.99+0.19               | 213±4                | 1.18±0.04         | 2.36±0.09           | 9.4±1.11              | 97.97±0.11      |
| LTF3           | 47.52+0.06    | 14.23+0.14               | 267±3                | 1.24±0.08         | 2.49±0.11           | 9.6±1.21              | 98.14±0.06      |
| LTF4           | 48.13+0.11    | 14.26+0.18               | 276±6                | 1.26±0.05         | 2.61±0.10           | 10.2±1.18              | 98.65±0.05      |
| LTF5           | 48.32+0.09    | 14.28+0.16               | 289±4                | 1.28±0.03         | 2.67±0.16           | 11.6±0.5              | 99.08±0.09      |
| LAF1           | 43.47+0.09    | 13.89+0.17               | 178±6                | 1.04±0.06         | 1.21±0.08           | 4.12±1.58              | 97.18±0.08      |
| LAF2           | 46.13+0.06    | 13.98+0.19               | 209±5                | 1.12±0.03         | 1.34±0.13           | 4.19±0.6              | 97.88±0.05      |
| LAF3           | 47.68+0.08    | 14.28+0.22               | 261±4                | 1.23±0.07         | 1.46±0.11           | 5.02±1.15              | 98.26±0.03      |
| LAF4           | 48.66+0.17    | 14.93+0.23               | 279±3                | 1.35±0.05         | 1.57±0.09           | 5.48±1.12              | 98.46±0.04      |
| LAF5           | 48.82+0.16    | 14.11+0.19               | 304±5                | 1.43±0.04         | 1.84±0.13           | 5.75±0.3              | 98.64±0.06      |

Figure 1: SEM photographs of MMMP prepared from Chitosan in combination with (A) Xanthan gum (B) Guar gum, (C) Tragacanth (D) Acacia showing magnifications of 100x, (E) Photograph of MMMP discs (F) MMMP in an enteric-coated capsule
Table 2: In vitro drug release kinetic data of LAN MMMP formulated

| Formulation | T50 (h) | T90 (h) | Zero order R2 | K0(mg.h⁻¹) R2 | First order R2 | K1(h⁻¹) R2 | Higuchi R2 |
|-------------|---------|---------|---------------|----------------|----------------|-------------|------------|
| LXF1        | 3       | 5       | 0.9699        | 15.048         | 0.5162         | 0.573       | 0.8222     |
| LXF2        | 3.5     | 6.5     | 0.9831        | 12.409         | 0.6552         | 0.383       | 0.8548     |
| LXF3        | 4.5     | 8       | 0.9931        | 10.208         | 0.7571         | 0.308       | 0.8981     |
| LXF4        | 5       | 9       | 0.9904        | 9.407          | 0.7619         | 0.291       | 0.8977     |
| LXF5        | 5.5     | 10      | 0.9899        | 8.178          | 0.8428         | 0.259       | 0.8851     |
| LGF1        | 3.5     | 6.5     | 0.9781        | 13.040         | 0.6676         | 0.384       | 0.8421     |
| LGF2        | 4       | 7.5     | 0.9866        | 11.073         | 0.6801         | 0.330       | 0.8674     |
| LGF3        | 5       | 9       | 0.9942        | 9.050          | 0.6729         | 0.293       | 0.9048     |
| LGF4        | 5.5     | 10      | 0.9918        | 8.457          | 0.7615         | 0.243       | 0.9048     |
| LGF5        | 6.5     | 11      | 0.9906        | 7.464          | 0.8932         | 0.170       | 0.9016     |
| LTF1        | 3.5     | 5.5     | 0.9790        | 13.749         | 0.6193         | 0.446       | 0.8440     |
| LTF2        | 4       | 7       | 0.9864        | 11.523         | 0.6152         | 0.365       | 0.8671     |
| LTF3        | 4       | 8       | 0.9894        | 10.554         | 0.6647         | 0.376       | 0.8880     |
| LTF4        | 5       | 9       | 0.9890        | 9.641          | 0.6822         | 0.284       | 0.8785     |
| LTF5        | 6       | 10.5    | 0.9924        | 7.872          | 0.9207         | 0.229       | 0.8871     |
| LAF1        | 4       | 7       | 0.9942        | 11.819         | 0.6997         | 0.375       | 0.9152     |
| LAF2        | 4       | 7.5     | 0.9959        | 10.793         | 0.6983         | 0.337       | 0.9006     |
| LAF3        | 4.5     | 8       | 0.9975        | 9.929          | 0.7045         | 0.324       | 0.9129     |
| LAF4        | 5       | 9.5     | 0.9975        | 8.767          | 0.7405         | 0.265       | 0.9163     |
| LAF5        | 5.5     | 9.5     | 0.9967        | 8.466          | 0.8644         | 0.204       | 0.9130     |

Figure 2: FTIR spectra
stretching vibration of –NH-, -CH₂, aromatic ring, C-O and ether bond, respectively (Dey et al., 2007). Similarly, the FTIR spectrum of formulation LXF5 showed the characteristic absorption peaks of LAN appeared at 3218.57, 2982.44 & 2928.86, 1578.79, 1281.37, 1114.52 denoting stretching vibration of –NH-, -CH₂, aromatic ring, C-O and ether bond, respectively. Further, the FTIR spectrum of formulation LGF5 showed the characteristic absorption peaks of LAN appeared at 3219.73, 2982.94 & 2928.92, 1579.37, 1281.34, 1114.22 denoting stretching vibration of –NH-, -CH₂, aromatic ring, C-O and ether bond, respectively. Again, the FTIR spectrum of formulation LTF5 showed the characteristic absorption peaks of LAN appeared at 3221.34, 2982.96 & 2929.32, 1578.73, 1281.22, 1114.55 denoting stretching vibration of –NH-, -CH₂, aromatic ring, C-O and ether bond, respectively. Finally, the FTIR spectrum of formulation LAF5 showed characteristic absorption peaks of LAN appeared at 3220.36, 2982.67 & 2929.69, 1579.33, 1281.02, 1114.69 denoting stretching vibration of –NH-, -CH₂, aromatic ring, C-O and ether bond, respectively (Muthusamy et al., 2005).

Differential scanning calorimetry (DSC) studies
The DSC thermograms showed an endothermic peak for pure lansoprazole at 181.36°C, which corresponds to the melting process. Thermogram of formulation LXF5 showed two endothermic peaks at 181.49°C and 267.56°C. Similarly, for formulation LGF5 two endothermic peaks were observed at 83.28°C and 181.24°C. Formulation LTF5 showed two endothermic peaks at 150.29°C and 181.29°C. The thermogram of formulation F9 indicated endothermic peaks at 181.49°C and 274.14°C (Figure 2). The distinct endothermic peaks in all formulations indicate that drug and polymers co-exist as a physical mixture and there is no interaction between them (Shidhaye et al., 2008).

In vitro dissolution studies
up to 12 h. Among formulations LXF5 showed extended drug release up to 98.85 ± 7.04% for 14 h; LGF5 94.07 ± 7.25% up to 12.5 h; LTF5 showed 99.04 ± 7.34% up to 12.5 h, and LAF5 showed 94.9 ± 4.39 up to 12 h compared to other formulations. In all the cases, the drug release was reciprocal to the polymer concentration in the formulations (Figure 3). The in vitro release time of LAN from all formulations was delayed significantly with an increase in polymer concentration. On the other hand, the increase of gums content resulted in a decrease in the amount of LAN released. The apparent slow-release of LAN from all these formulations during the release study seems to be dependent on the drug: polymer ratio. The f-ratio value and p-values obtained for xanthan, guar, trag-
gacanth and acacia gums were 2.70775, 0.040516; 2.91575, 0.029336; 2.63078, 2.63078; and 2.8205, 0.030824 respectively. The result was significant at p<0.05. The mechanism of drug release for the above formulations was determined by calculating the correlation coefficient (R² value) for the kinetic models, as summarized in the above discussion. All the formulations followed zero-order drug release kinetics. The ‘n’ values of Korsmeyer–Peppas model for the best formulations were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was found to be non-Fickian diffusion or anomalous diffusion for the formulations tested. The time required for dissolution of 50% (T₅₀) and 90% (T₉₀) were determined. It was seen that the duration of release gradually increased with an increase in natural polymers proportion, as against chitosan. Formulations FXF5, FGF5, FTF5 and FAF5 showed a higher rate of drug release compared to that of other formulations of respective polymers. Among all natural polymers employed in this specification, the decreasing order of drug release from the polymers is as Xanthan gum > Tragacanth > Guar gum > Acacia.

Stability studies
Accelerated stability studies showed no significant change in the appearance of the patches studied. Student t-test was conducted on drug content and the p-values obtained were 0.3216, 0.4138, 0.3141 and 0.4221 for formulations LXF5, LGF5, LTF5 and LAF5 respectively which were lesser than the table value of 2.57 at 95% confidence limits and hence the result is not significant at p<0.05. There was no significant difference observed in the drug content uniformity before and after the stability studies. Student t-test was conducted on drug dissolution before and after stability testing for optimized formulations. The p-values obtained were 0.436992, 0.419959, 0.429062 and 0.435343 for formulations LXF5, LGF5, LTF5 and LAF5 respectively which were lesser than the table value of 2.57 at 95% confidence limits and hence the result is not significant at p<0.05. There was no significant difference observed in the drug dissolution before and after the stability studies. Similarity factor (f²) for optimized formulations LXF5, LGF5, LTF5 and LAF5 compared before and after stability testing was found to be 85, 80, 86 and 85 respectively which were between 50 and 100. Therefore the dissolution profiles of optimized formulations before and after stability testing are considered to be similar.

The results of various properties of prepared formulations were summarized in Table 2. Texture of patches appeared rough surface for those prepared using xanthan gum and acacia; whereas those prepared using guar gum and tragacanth showed a nearly smooth surface.

CONCLUSIONS
This learning deliberates the groundwork of MMMP of LAN using natural polymer chitosan with xanthan gum, guar gum, tragacanth or acacia. The kind of polymer exaggerated the drug statement rate and the device. Polymer swelling is vital in influencing the drug announcement rate inauguration. The order of drug release with respect to selected polymers was found as xanthan gum > tragacanth > guar gum > acacia. The optimized formulations, LXF5, LGF5, LTF5 and LAF5, offered best-controlled release along. Great Dependability might have been watched for three months throughout accelerated soundness investigations. Since those detailing indicated addition discharge to prolonged period, those measurement Might be decreased, and the could be allowed inadequate absorption of the medication regardless Might be avoided.

Conflict of Interest
The authors declare that they have no conflict of interest for this study.

Funding Support
The authors declare that they have no funding support for this study.

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