JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

# Development and evaluation of time controlled pulsatile release Lisinopril tablets

**Basawaraj S.Patil*, Abhishek M Motagi, Upendra Kulkarni, Hariprasanna R.C., Shivanand A. Patil**

PG Department of Pharmaceutics, R.M.E.S College of Pharmacy, Gulbarga 585102 – Karnataka

**ABSTRACT:**

The objective of present investigation was prepare and evaluate a oral pulsatile drug delivery system based on a press coated tablet, where a core tablet surrounded coating material. The system consists of two parts, a core tablet containing the active ingredient and other excipeients, and coating materials consist of hydrophilic and hydrophobic polymer. The core containing Lisinopril as a bioactive compound was prepared by direct compression method and evaluated for thickness, hardness, weight variation and friability. The coating materials consisted of hydrophobic polymer of ethyl cellulose and hydrophilic materials (HPMC 15 CPS) were used in different concentration. The tablets prepared were evaluated for micromeritic properties (bulk density, tapped density, Angle of repose and carr's index), hardness, thickness, weight variation, friability, drug content uniformity and *in-vitro* drug release study. The drug-excipient study was carried out by using FTIR. *In-vitro* drug release studies were carried out using pH 7.4 phosphate buffer for 12 hrs. From the obtained results, formulation LC2 was selected as an optimized formulation for designing pulsatile device.

**Key words:** Lisinopril, Pulsatile drug delivery system, lag time, press coated tablets, HPMC 15 cps.

Article history:
Received 02 Feb 2012
Accepted 07 Feb 2012
Available online 13Feb 2012

**For Correspondence:**

*Basawaraj S.Patil*

*Professor*

*PG Department of Pharmaceutics,*

*R.M.E S's College of Pharmacy, Old Jewargi Road,*

*Gulbarga-585102 Karnataka*

*Email:bspatilglb17@rediffmail.com*

(www.jpsbr.org)

## INTRODUCTION:

Recent studies in the area of oral controlled drug delivery include novel approaches, which prolong the GRT and Chronotherapeutic delivery system which release the drug in a pulsatile fashion, is recently gaining much attention worldwide. Pulsatile drug delivery system are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time[1].Various diseases like asthma, hypertension, and arthritis show circadian variation, that demand time scheduled drug release for effective drug action for example inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day. Result of several epidemiological studies demonstrates the elevated risk of several pathologies during a 24 h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Ischemic disease such as angina pectoris and myocardial infarction, and manifested more frequently during these times. Blood pressure which arises notably just before waking up is usually responsible for these attacks. To follow this principle one must have to design the dosage forms so that it can be given at the convenient time for example bed time for the above mentioned diseases with the drug release in the morning. Using current release technology, it is possible for many drugs oral delivery for a pulsed or pulsatile release, which is defined as the rapid and transient release of a certain amount of drug within a short time-period

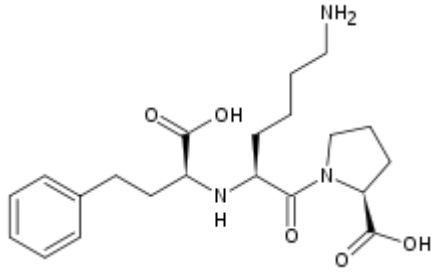

**Figure. 1:** Structure of Lisinopril

immediately after a predetermined off-release period. Chronotherapeutical devices based on multiphase drug release were achieved by using a three layer tablet while similar devices were also developed. Time controlled coating system was also developed including single and multiple unit dosage forms[3]. The concept of the multiple unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates, which include mini tablets, pellets and granules[4]. These systems provide flexibility during formulation development and gives therapeutic benefits to patients. A significant advantage of multiparticulates is that they can be divided into desired doses without making formulation or process changes. They can also be blended to deliver simultaneously incompatible bioactive agents or particles with different drug release properties. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single unit [5]. Single unit dosage forms are defined as oral delivery systems that consist of one unit that contains a single dose of the drug and is intended to be administered singularly. Many single unit dosage forms have been developed for the modified release of bioactive materials. The most widely investigated example is the monolithic matrix based tablet. The advantages of this dosage form include high drug loading and the availability of well characterized and cost-effective production methods. Drug release from these systems is controlled by a variety of mechanisms, including drug diffusion, tablet erosion, matrix swelling or a combination of these mechanisms. Film coated and osmogen controlled single unit dosage forms have also been studied for modified release applications. Single unit includes Capsules, Coated tablets, Osmotic Pumps, Insoluble matrix tablets, soluble matrix tablets, degradable matrix tablets and ion exchange resins.

Lisinopril (Fig. 1), is a synthetic peptide derivative, is an oral long –acting angiotensin converting enzyme inhibitor (ACE) [6]. It is widely used in treatment of hypertension; it has the biological half-life of 12.6 hr. Its bioavailability is 25% and it is mainly excreted in urine[7, 8].

Therefore, in this present research investigation an attempt will be made to formulate time controlled Lisinopril pulsatile tablets. The proposal consists of a core tablet coated with two layers an inner swelling layers and outer rupturable layer.

**Table 1:** Formulation of core tablets

| Ingredients | Quantity (mg) |
|---|---|
| Lisinopril dihydrate | 10 |
| Crosscarmalose sodium | 3 |
| Mannitol | 35 |
| Talc | 1 |
| Magnesium Stearate | 1 |
| Total | 50 mg |

Study an attempt has been made to formulate pulsatile tablets of Lisinopril by direct compression method.

**MATERIALS AND METHODS**

Lisinopril dihydrate was gift sample from Unimerk Remedis Pvt. Ltd. Gujarat. Ethyl cellulose, HPMC 15cps, crosscarmalose sodium, mannitol, talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

**FTIR Studies:**

Compatibility studies were carried out to know the possible interaction between Lisinopril and excipients used in formulations. Drug polymer compatibility studies were carried out using FT-IR spectroscopy (JASCO FT/IR-5300). IR spectrums of pure drug and polymers were observed between 400-4000 $cm^{-1}$.

**Stability studies:**

Short term stability studies were performed at temp of 40 $\pm 2^0$C / 75$\pm$ 5% RH over a period of three month (90 days) on the promising press coated tablets of Lisinopril ( formulation LC2). Sufficient number of tablets (15) were packed in amber coloured rubber stopper vials & kept in stability chamber maintained at 40 $\pm 2^0$C / 75$\pm$ 5% RH. Samples were taken at one month intervals for the drug content estimations. At the end of three month period, dissolution test was performed to determine the drug release profiles.

**Preparation of tablets**

**Preparation of Core tablets: [9]**

The core tablet was made of 50 mg of pure drug Lisinopril, mannitol, crosscarmalose sodium, talc, magnesium stearate which was compressed directly using 6 mm flat punch (Table 1).

**Preparation of Press coated tablets by direct compression method: [9]**

As given in the table 2, an impermeable coating consisting of ethyl cellulose, and HPMC 15 cps was applied under the bottom and around the core tablet. The mixture 10 % of two

**Table 2:** Formulation of press -coated tablets. (HPMC 15cps + Ethyl cellulose)

| Ingredients(mg) | LC1 | LC2 | LC3 | LC4 | LC5 |
|---|---|---|---|---|---|
| Lisinopril Core tablet | 50 | 50 | 50 | 50 | 50 |
| HPMC 15 cps | 200 | 150 | 125 | 100 | 50 |
| Ethyl cellulose | 50 | 100 | 125 | 150 | 200 |
| Total | 300 | 300 | 300 | 300 | 300 |

**Table 3:** Result of pre-compression parameter for Lisinopril powder blend

| Parameter | Observation |
|---|---|
| **Angle of Repose(θ)*** | $24^0 \pm 1.09$ |
| **Bulk density*** | $0.4166 \pm 0.15$ gm/cm$^3$ |
| **Tapped bulk density*** | $0.4545 \pm 0.20$ gm/cm$^3$ |
| **Carr's Compressibility Index (%)** | $8.338 \pm 0.58$ (%) |
| **Hausner's ratio** | $1.0909 \pm 0.67$ |

*Average of three replicates

polymers was filled into a die of 9 mm diameter and then gently compacted to make a powder bed with a flat surface. The core tablet was carefully placed in the center of the powder bed; the die was filled with the remaining quantity of coating powder (90%) so that the surrounding surfaces of the core tablet were fully covered. The bed was compressed directly by using 9 mm flat punch. (Rimek Mini Press-I), to produce the desired press coated tablets.

**Evaluation of tablets**

Tablet was evaluated for hardness, friability, weight variation, thickness, drug content, *In vitro* dissolution studies and stability study. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Thickness of tablets was determined by using dial caliper. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 10 mg of Lisinopril was taken and dissolved in phosphate buffer 7.4. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 210 nm. Using 900 ml of buffer monitored *in vitro* dissolution of Lisinopril from tablets at 37 ± 0.5$^0$C at 100 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 hour time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 210 nm. The stability study of the tablets were carried out according to ICH guidelines by storing tablets in stability chamber at 40 ± 2$^0$ C / 75 ± 5% RH for 3 months

**Table 4:** Pre-Compression parameters for coating materials

| Formulation code | Bulk density* (g/cc) ± SD | Tapped density (g/cc) ± SD | Angle of repose* (degree) ± SD | Carr's index *(%) ± SD | Hausner's ratio ± SD |
|---|---|---|---|---|---|
| **LC1** | 0.5342 ± 0.13 | 0.6408 ± 0.01 | 26.38 ± 1.35 | 16.6354 ± 0.67 | 1.1999 ±0.03 |
| **LC 2** | 0.5088 ± 0.01 | 0.5941 ± 0.01 | 26.01 ± 0.13 | 14.3578 ± 1.51 | 1.1676 ±0.01 |
| **LC3** | 0.5147 ± 0.02 | 0.6091 ± 0.02 | 27.01 ± 1.21 | 15.4982 ± 1.59 | 1.1834 ±0.02 |
| **LC4** | 0.5218 ± 0.03 | 0.6218 ± 0.02 | 25.08 ± 1.07 | 16.0823 ± 1.19 | 1.1916 ±0.01 |
| **LC 5** | 0.5401 ± 0.04 | 0.6387 ± 0.02 | 28.46 ± 1.26 | 15.4376 ± 1.08 | 1.1825 ±0.02 |

*Average of three replicates

**Table 5:** Result of post-compression parameter for core tablet

| Parameter | Observation |
|---|---|
| Thickness* | 2.14 ± 0.45 mm |
| Hardness* | 2.00 ± 0.25 kg/cm$^2$ |
| Average Weight | $49.16 \pm 0.47$mg |
| Friability (%) | $0.7415 \pm 0.78$ (%) |

*Average of three replicate

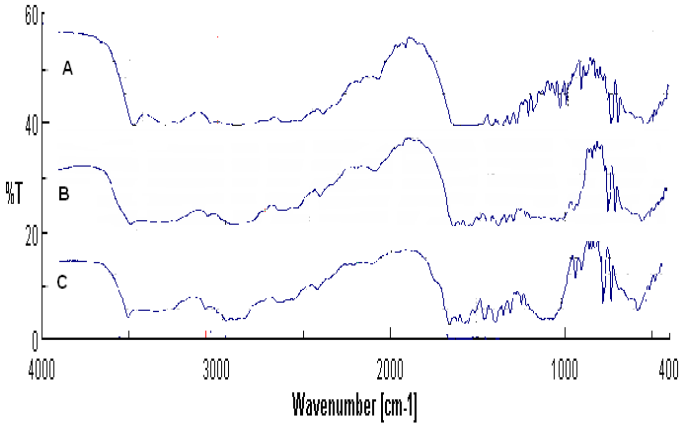


**Figure 2:** IR spectrum of Lisinopril (A), Lisinopril+ Ethyl Cellulose (B), Lisinopril + HPMC 15 cps (C)

**RESULTS AND DISCUSSION**

The compatibility of drug with other ingredients was checked by FTIR studies, these results revealed that there was no interaction between drug and other excipients (Fig 2). The flow properties of the powder mixture are important for the uniformity of mass of tablets; the flow of powder mixture was before compression of tablets.

**Table 6:** Post-compression parameters for press coated tablets

| Formulation Code | Hardness ($kg/mg^2$) ±SD | Thickness (mm) ±SD | Friability (%) ±SD | Weight Variation ±SD | Drug Content (%),±SD |
|---|---|---|---|---|---|
| **LC1** | 5.00 | 5.31 ± 0.09 | 0.79 ± 0.01 | 299.4 ± 0.7 | 97.23 ± 1.25 |
| **LC 2** | 5.00 | 5.23 ± 0.09 | 0.69 ± 0.09 | 298 ± 0.08 | 99.01 ± 0.25 |
| **LC3** | 5.50 | 5.30 ± 0.07 | 0.68 ± 0.07 | 299.5 ± 0.6 | 97.78 ± 1.18 |
| **LC4** | 5.50 | 5.32 ± 0.03 | 0.75 ± 0.08 | 297 ± 0.07 | 98.89 ± 1.06 |
| **LC 5** | 5.50 | 5.83 ± 0.09 | 0.83 ± 0.07 | 298 ± 0.08 | 97.99 ±1.89 |

**Table 7:** Kinetic values obtained from *in-vitro* release profile for pulsatile tablets

| Formulation Code | Zero order kinetic data Regression coefficient (r) | First order kinetic data Regression coefficient (r) | Higuchi Matrix kinetic data Regression coefficient (r) | Peppas kinetic data | |
|---|---|---|---|---|---|
| | | | | Regression coefficient (r) | Slope 'n' |
| **LC1** | 0.7656 | 0.9500 | 0.8529 | 0.6741 | 0.2473 |
| **LC2** | 0.7612 | 0.9328 | 0.8424 | 0.7361 | 0.2084 |
| **LC3** | 0.7548 | 0.8872 | 0.8292 | 0.7938 | 0.1813 |
| **LC4** | 0.7339 | 0.9008 | 0.8295 | 0.7797 | 0.1576 |
| **LC5** | 0.7293 | 0.8640 | 0.8218 | 0.7530 | 0.1515 |

**Table8:** Drug content data of stability formulations LC2

| Sr. No | Formulation code | 1st day (%) | 30th day (%) | 60th day (%) | 90th day (%) |
|---|---|---|---|---|---|
| 1 | **LC2** | 99.10 | 99.78 | 99.25 | 98.57 |

**Table 9:** *In-vitro* drug release data of the stability formulation LC2

| Sr. No | Time (hr.) | Cumulative% Drug release± SD 40± 1°C 1st day | 30th day | 60th day | 90th day |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 1 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 2 | 0.29 | 0.27 | 0.46 | 0.31 |
| 3 | 3 | 1.23 | 1.03 | 1.57 | 1.16 |
| 4 | 4 | 2.36 | 2.17 | 2.75 | 2.56 |
| 5 | 5 | 71.45 | 70.41 | 72.41 | 71.11 |
| 6 | 6 | 81.93 | 82.42 | 80.10 | 83.19 |
| 7 | 7 | 92.01 | 91.92 | 90.11 | 92.17 |
| 8 | 8 | 95.28 | 94.46 | 95.19 | 96.37 |
| 9 | 9 | 99.10 | 99.92 | 99.01 | 99.28 |

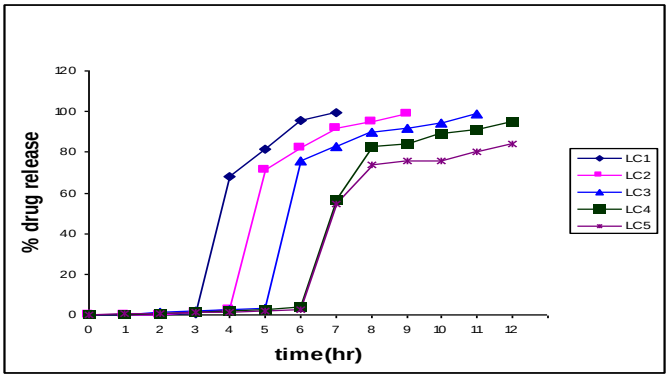


**Figure 2:** Zero order plots of formulation containing HPMC 15 CPS (LC1 –LC5)

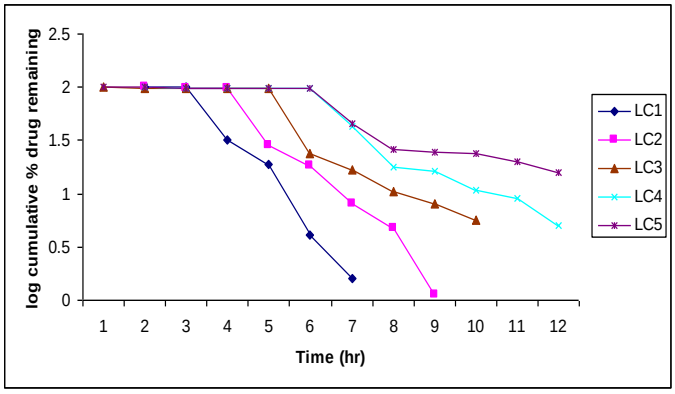


**Figure 3:** First order plots of formulation containing HPMC 15 CPS (LC1 –LC5)

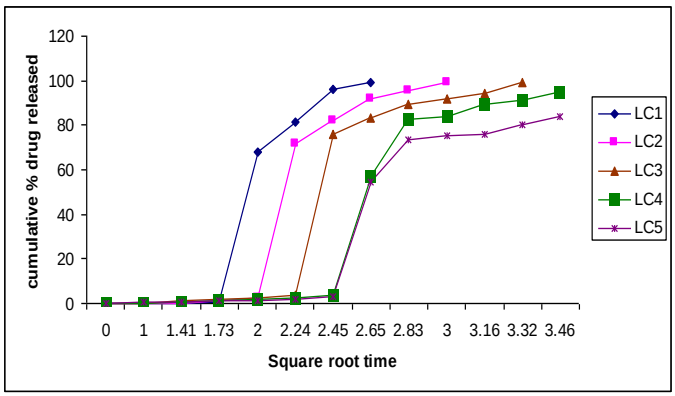


**Fig. 4:** Higuchi diffusion plots of formulation containing HPMC 15 CPS (LC1 –LC5)

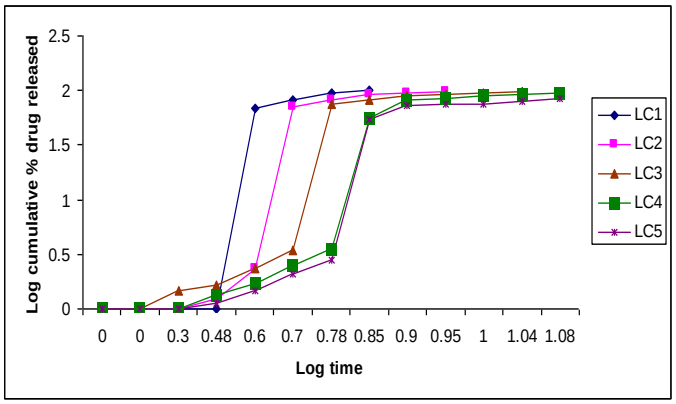


**Fig. 5:** Peppas exponentional plots of formulation containing HPMC 15 CPS (LC1 –LC5)

The values of pre-compression parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 3 and 4. The post compression parameters results are shown in table 5 and 6. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be uniform in all formulations. The tablet thickness was found to be 5.12 to 5.31 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5 %, which provide good uniformity in all formulations. *In vitro* release profiles of different formulations are shown in Fig. 6. With formulation formulations LC1, LC2, LC3, LC4 and LC5 the lag time was1 – 6 and drug release was found 99.37 %, 99.10 %, 99.00 %, 95.00 % and 84.00 %.

*In vitro* dissolution results elicited that 84 %to 99.78 %drug released after lag time was observed in all formulations. But maximum lag time (hr) was observed in formulation LC5. Hence LC2 was considered as the optimum formulation.

*In vitro* dissolution results elicited that 84 % to 99.78 % drug released after lag time was observed in all formulations. But maximum lag time (hr) was observed in formulation LH5. Hence LH3 was considered as the best formulation.

Data obtained from the *in-vitro* release studies were subjected to Kinetic treatment to know the order of release. The 'r' values for zero order, first order, higuchi and peppas are given in table 7 and shown in Fig. 3 to 6. In the present study the release profiles were non-linear suggesting that the drug release from the formulations wasnot zero order that was confirmed by low 'r' values of 0.7293 – 0.7656. Higuchi plots of all the formulations were non linear because 'r' values are not near about 1 in all the cases. The formulations were subjected to peppas plots by taking log cumulative % drug released versus log time. The plots are found fairly linear and slope value was calculated (n value) which was in ranges of 0.1515 to 0.2473 for LC1 – LC5 indicating the drug was released by Fickian diffusion mechanism. Stability studies results revealed that, there is no change in drug content and *in-vitro* drug release are shown in table 8 and 9.

**Conclusion**

From the above results, it can be concluded that the prepared pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutic management of hypertension.

**ACKNOWLEDGEMENTS**

The authors are thankful to Unimerk Remedis Pvt. Ltd. Gujurat, for providing gift sample and also very much thankful to Prof. Kishoresingh K.Chatrapathi President, R.M.E.S's College of Pharmacy Gulbarga, for his valuable support and providing necessary facilities to carry out the research work.

**REFERENCES**

1. Susan A. Charman and William N. Charman. Oral Modified Release Delivery Systems. In: M.J.Rathbone Ed. Modified Release Drug Delivery Technology, New York; Marcel Dekker, vol126, p1-10. (2003).
2. British Pharmacopoeia. The stationary office, MHRA, British pharmacopoeial commission office, London, Vol 3, page no- 2233, (2007).
3. Zou, H.; Jiang, X.; Kong, L.; Gao, S. Design and evaluation of a dry coated drug delivery system with floating-pulsatile release. J. Pharm. Sci. 2008; 97:263-273.
4. The Indian Pharmacopoeia. Ministry of Health and Family Welfare, Govt. of India. The Controller of publication: New Delhi, 1996; 2: 736.

5. Banker, G. S.; Anderson, N. R. Tablets. The theory and practice of industrial pharmacy;Lachman, L., Lieberman, H. A., Kanig, J. L., Eds.; 3rd; Varghese Pub. House: Bombay, 2003, p 297-299.
6. Anupam Nayak S, Ashish Jain , Priyanka Rathore, Sumbate S, Nayak S.A Comparative study of Lisinopril from different vehicle Int.J.of pharmacy & pharma.sci. 2009; 1:213-218.
7. Guda A, Gudas GK, Bingi M, Subal D, Rajesham VV. Design and evaluation of controlled release mucoadhesive buccal tablets of Lisinopril. Int.J.pharma.Res. 2010; 2(4): 24-27.
8. Bussemer T, Bomeier R. Formulation parameters affecting the performance of coated gelatin capsules with pulsatile release profiles Int.J. Of pharma. 2003; 267:59-68.
9. Efentakis M, Koligliati S, Vlachou M. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. Int J Pharm.2006; 311:147-56.