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Research Article

PREPARATION OF LOPERAMIDE HYDROCHLORIDE CHEWABLE TABLET: METHOD VALIDATION BY HPLC

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ABSTRACT

Recent years have seen an ever increasing interest in application of novel materials in solid dosage form. Loperamide hydrochloride [4-(p-chlorophenyl)-4-hydroxy-N, N-dimethyl-diphenyl-1-piperidine butyramide hydrochloride], is an opiate agonist widely used as an effective drug for the control and symptomatic relief of acute non-specific diarrhea. The present work aimed to prepare Loperamide hydrochloride chewable tablet in combined with simethicone and develop a new sensitive and specific analytical procedure by HPLC suitable for application in a drug quality control. Loperamide chewable tablets were prepared by wet granulation technique and it has been found that the prepared tablets showed good physical characteristics, drug content and percentage of drug release. Among the 6 formulations F 1 showed better drug release (96%) and drug content (98.38%) than other formulations. Method of non-aqueous granulation and adsorption of simethicone to dry powder blend improved hardness and provides good physical appearance to the tablets. Addition of Loperamide hydrochloride to binder solution and using proper amount of surfactant (SLS) increased content uniformity and better dissolution of Loperamide hydrochloride. Further, F 1 was selected for the method development and validation purpose. The validation data indicates the suitability of the developed chromatographic method which is easier and cost effective than the other reported and official methods.

Keywords: Loperamide hydrochloride, Simethicone, Chewable tablets, HPLC

INTRODUCTION

Loperamide is an anti-diarrhoeal agent. It has direct antisecretory effect on myentericopiate receptors in the gut[1]. Loperamide has minimal systemic availability (0.3%), with most of the drug being removed by first-pass metabolism[2], which further supports a local action in the gut. The main objective of the study is to investigate the best suitable dosage form of Loperamide in combination with simethicone and its method validation by HPLC. Historically, in preparing solid simethicone dosage forms, difficulties have been encountered when attempting to incorporate substantial quantities of liquid simethicone to solid final blend such as insufficient flow ability, hardness of tablet and not uniform distribution throughout the formulation produce irregular release of drug. Adsorption of simethicone to the powder blend and wet granulation techniques are used to prepare Loperamide chewable tablet which can overcome those difficulties. Loperamide chewable tablet are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact.

MATERIALS AND METHODS

Loperamide Hydrochloride was gifted by Lake Chemicals Pvt. Ltd. All other chemicals and reagents used were of analytical grade. Chemicals used along with supplier details are as follows Microcrystalline cellulose (Avicel ph-102; FMC Biochemical), Lactose monohydrate and Lactose DCL-21 (DMV Fonterra), Povidone K 30 (PVP K 30; BASF), Cross carmellose sodium (premillose; Kawarlal & Co), Cross povidone XL-10 (ISP INDIA), Sodium lauryl sulphate (Bendale Chemicals), Hydroxyl propyl cellulose (klucel LF; Signet), Colors (Roha Die), Flavors (Givaudan), Aspartame (BIOCON), Simethicone (Delta Chemicals), Colloidal silicon dioxide (Aerosil; K.P. Mnish & Global Ingredients) and Magnesium stearate (Amishi Drugs & Chemicals).

Preparation of Loperamide chewable tablets

Chewable tablets containing 2 mg Loperamide were prepared with a total tablet weight of 1100 mg by wet granulation method. The Loperamide and Simethicone granules were prepared separately. Quantity of Loperamide and excipients are given in Table 1. The required excipients were sieved and mixed at a slow speed in "Rapid Mixer Granulator" to get a dry mix then simethicone were adsorbed to the dry blend for simethicone granules. Povidone K 30 and erythrosine supra, hydroxyl propyl cellulose and sodium lauryl sulphate were dissolved in purified water to get a binder. In case of Loperamide granules, the required excipients were sieved and mixed at a slow speed to get a dry mix. Loperamide and sodium lauryl sulphate added to binder solution of povidone. Both the dry mix was added to binder solution separately, granulated and the obtained wet mass was dried in "Fluidized bed dryer" at 70°C. Dried granules were sieved through 20# mesh sieve. Excipients like lactose DCL, cross carmellose sodium, aerosil, lubricant and flavoring agents were then added to get a blend which was assessed for its flow properties. Blend with good flow property was Compressed by 19.2 X 8.9 mm oblong with 'ML' embossed on one side while other side plain punch in a 16 station compression machine (Cadmach, Ahmadabad) to get tablets.

Evaluation of tablet

Hardness

The hardness test is performed to provide a measure of tablet strength. Tablets should be hard enough to withstand packaging and shipping but not so hard as to create undue difficulty upon chewing. The hardness of the tablets was determined using Monsanto hardness tester[3]. It is expressed in kg/cm^2.

Disintegration

This test initially may not appear appropriate for chewable tablets as these tablets are to be chewed before being swallowed. However, patients, especially pediatric and geriatric, have been known to swallow these chewable dosage forms. This test would thus indicate the ability of tablet to disintegrate and still provide the benefit of the drug if it is accidentally swallowed. The disintegration time of tablet was measured in water (37^{0}C) according to USP Disintegration test apparatus. Three trials for each batch were performed[4, 5].

Weight variation and friability test

Weight variation test was performed by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average. Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for this purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of tablets were placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight[4, 5].

Table 1: Formulation of Loperamide Hydrochloride Chewable Tablets

Sl. No	Ingredients	Weight of each tablet in various formulations (1100 mg)					
		F 1	F 2	F 3	F 4	F 5	F 6
Loperamide granules							
1	Loperamide HCl	2.12	2.12	2.12	2.12	2.018	2.06
2	Lactose monohydrate	50.00	50.00	50.00	50.00	-	50.00
3	Microcrystalline cellulose(avicel ph102)	50.00	50.00	50.00	50.00	-	50.00
4	Crosscarmellose sodium	10.00	10.00	10.00	10.00	20.00	10.00
5	Erythrosine lake	0.10	0.10	0.10	0.10	0.10	0.10
6	Sodium lauryl sulphate	2.00	2.00	2.00	2.00	8.00	-
7	Povidone K-30	5.00	5.00	5.00	5.00	-	5.00
8	Isopropyl alcohol+methylene chloride	qs	qs	qs	qs	Qs	qs
Simethicone granules							
9	Microcrystalline cellulose(avicel ph102)	400.00	400.00	400.00	400.00	380.92	400.59
10	Lactose monohydrate	155.00	155.00	155.00	157.00	200.00	157.00
11	Aerosil-200	70.00	70.00	70.00	70.00	80.00	70.00
12	Crosscarmellose sodium	40.00	40.00	40.00	40.00	40.00	40.00
13	Crospovidone XL-10	10.00	10.00	10.00	10.00	10.00	10.00
14	Sodium lauryl sulphate	6.00	8.00	8.00	8.00	8.00	8.00
15	Simethicone	130.71	130.71	130.71	130.71	130.71	125.00
16	Hydroxyl propyl cellulose(Klucel LF)	10.00	10.00	10.00	10.00	10.00	10.00
17	Povidone K-30	25.00	25.00	25.00	25.00	30.00	10.00
18	Erythrosine supra	0.250	0.250	0.250	0.250	0.250	0.250
19	Sodium lauryl sulphate	2.00	-	-	-	-	-
20	Polysorbate 80	-	11.0	11.0	-	-	-
21	Purified water	qs	qs	qs	qs	qs	qs
Extra granulating materials							
22	Lactose DCL-15	63.82	52.82	70.72	70.72	130.00	95.00
23	Aspartame	20.00	20.00	20.00	20.00	8.00	4.00
24	Neotame	-	-	1.20	1.20	-	-
25	Peppermint flavor	4.00	4.00	4.00	4.00	6.00	4.00
26	Vanilla flavor	4.00	4.00	4.00	4.00	6.00	4.00
27	Crosscarmellose sodium	20.00	20.00	20.00	20.00	10.00	10.00
28	Colloidal silicon dioxide	10.00	10.00	10.00	10.00	10.00	10.00
29	Magnesium stearate	10.00	10.00	10.00	10.00	10.00	10.00

Chromatographic system and conditions for assay

The chromatographic system consisted of a JASCO (Japan) chromatograph equipped with an LC – Net II/ADC, an MU – 2010 Plus PDA Detector, a PU – 2089 Plus quaternary pump, an online degasser and a Rheodyne model 7725 injector valve with 50 µl sample loop. The chromatograph is coupled with "Chrompass" software. Separation was done on a HiQ Sil C18HS (250mm x 4.6mm, Particle size 5 µm) under reverse phase partition chromatographic conditions. The reverse phase column maintained at 25ºC. The mobile phase consisted of a mixture of acetonitrile: buffer (55:45).The buffer prepared by dissolving 1.08 gm sodium octane sulfonate in 1000 ml of water, 0.5 ml of triethylamine and 1 ml of 25% ammonia. The pH was adjusted to 3.2 using dilute orthophosphoric acid[6, 7]. The flow rate was 1.5 ml/min and the injection volume was 20 µl.

Preparation of stock solution, working solution and calibration curve

Accurately 0.01 gm of standard Loperamide was weighed and transferred to a 100 ml volumetric flask. The standard Loperamide was dissolved with 75 ml diluents (mixture of acetonitrile and water in the ratio 55:45), shaken and sonicated to dissolve, and volume was made up to 100 ml with the diluents. The stock solution was diluted further with diluents to obtain six working solutions with concentrations of 1-5 µg/ml. The prepared samples were also filtered through 0.45 µm nylon filter membrane before injection. The standard calibration curve was plotted by AUC Vs Concentration at 226 nm.

Assay of tablet

Twenty tablets were weighed, triturated to a fine powder. Equivalent amount of 10mg of Loperamide was transferred to a 100ml volumetric flask and 75 ml diluents (mixture of acetonitrile and water in the ratio 55:45) was added, shaken for 10 mins, sonicated for 15 mins to dissolve , volume was made up to mark with the diluents. The solution was filtered through whatman filter paper no. 41, then with 0.45 µm nylon filter membrane before injection[8, 9].

Method Validation

The developed methods were validated according to ICH guidelines. The validation parameters were linearity, specificity, accuracy, and precision, Limit of detection (LOD), Limit of Quantification (LOQ) and Robustness[10]. Intra-day and Inter-day precision values were estimated by assaying the pharmaceutical dosage form containing three different concentrations of Loperamide six times on the same day and on three different days. Accuracy was determined by recovery study by standard addition method. The standard was added to a predetermined concentration at 25%, 50% and 100% level. The LOD and LOQ was determined by using equation (1) and (2) respectively

$$LOD = 3.3\ \sigma / S \quad (1)$$

$$LOQ = 10\ \sigma / S \quad (2)$$

Where 'σ' is the standard deviation of y-intercept and 'S' is the slope of calibration curve.

In vitro dissolution testing

Dissolution study

The development and validation of the dissolution test was performed using USR-XX 8 basket dissolution apparatus (Electro Lab. TDT 06P). All the dissolution samples were analyzed by HPLC assay.

Chromatographic system and conditions for dissolution study

The chromatographic analysis was performed at room temperature, using C_{18} reverse phase column. The mobile phase consisted of a mixture of acetonitrile: buffer (55:45). The flow rate was maintained at 1.5 ml/min and the injection volume was 50 µl.

Solubility determination and sink conditions

The sink conditions were determined in different media. HCl 0.1 N, HCl 0.01 N, H_2O + 0.1% sodium lauryl sulfate, phosphate buffer pH 6.0 and acetate buffer pH 4.0 were tested. Vessels (n = 6) containing 900 ml of 0.1% sodium lauryl sulfate in 0.1N hydrochloric acid, pre-heated to 37ºC before adding Loperamide Hydrochloride. The dissolution was carried out in USP apparatus II at 75 rpm for 45 mins. An aliquot (10 ml) was removed from each vessel after 15, 30 and 45 mins and filtered in 0.45 µm nylon filter membrane before injection.

RESULTS AND DISCUSSION

Results of physical characteristics of Loperamide chewable tablets of all 6 formulations are listed in Table 2. F 1 formulation had thickness around 7.28 - 7.29 whereas thickness of F 2, F 3, F 4, F 5 and F 6 in the range of 7.00 to 7.13. However, all the formulations were within the range ±5% variation of standard value. Weight variation test ranges shows all formulations passed weight variation test as the % weight variation was within the limits of 5% and F 1 had less weight variation among the 6 formulations. Hardness value of F 2, F 3, F 4 and F 6 are in the range of 7 to 9 Kg. The maximum hardness was obtained for batch F 1 which is 9 to 10 kg which indicates adequate mechanical strength. The maximum and minimum friability among the 6 formulations were found to be 0.200% and 0.110% respectively. However F 1 had the least friability. The percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. Disintegration time ranges from 12 to 18 min. The tablets of batch F 5 and F 6 disintegrated rapidly (i.e. in 12 min.) than any other batch which indicate as the hardness of tablet increased disintegration time decreased. Dissolution of Loperamide Hydrochloride chewable tablets varied depending upon the type of excipient used (Table No 1). Formulation F 1 containing the lactose DCL 6.00% was found to be satisfactory than other formulations, which showed good physical characteristics, drug content and percentage of drug release than other formulations (Table 2). So, formulation F1 was used for the method development and validation purpose.

Table 2: Evaluation of Loperamide hydrochloride Chewable Tablets

Evaluation parameter	F 1	F 2	F 3	F 4	F 5	F 6
Thickness (mm)	7.28-7.29	7.00-7.10	7.10-7.13	7.00-7.10	7.00-7.04	7.06-7.09
Hardness (Kg/cm2)	9.00-10.00	8.00-9.00	8.00-9.00	8.00-9.00	4.00-5.00	7.00-8.00
Average Weight (mg)	1106.80	1101.00	1100.00	1101.00	1097.30	1099.00
Friability (%)	0.110	0.200	0.200	0.139	0.138	0.167
Disintegration time (mins)	18.00	16.00	14.00	15.00	12.00	12.00
Drug Content (%)	98.38	95.40	96.20	95.00	90.00	90.50
Cumulative drug release (%)	96.00	89.50	90.50	88.00	72.90	75.40

Table 3: Assay of F 1 Formulation

Trial no. of the formulation F1	Label claim (mg)	Assay (Mean*) (%)	Mean*±R.S.D.
T1	2	98.2	
T2	2	97.1	98.38 ± 1.04
T3	2	97.4	
T4	2	99.5	
T5	2	98.5	
T6	2	99.6	

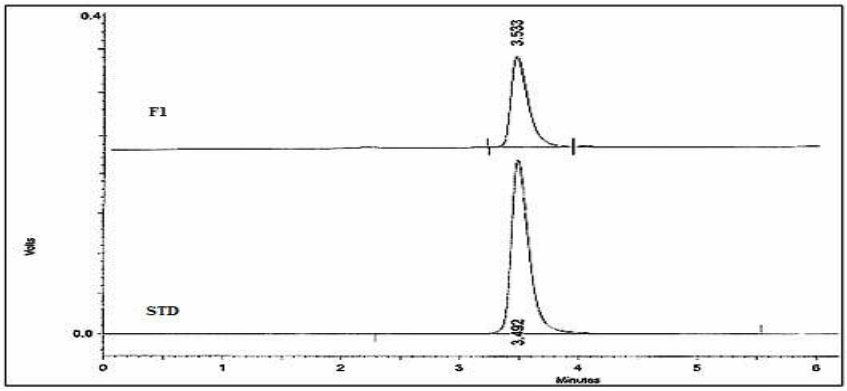

Fig. 1: Assay of Loperamide hydrochloride of F 1 formulation

The prepared tablets were assayed by the above mentioned chromatographic method and the results were expressed and evaluated in terms of relative standard deviation (Table 3), which is found to be lower than 2 (±1.04). The chromatogram shows the retention time 3.55 ± 0.02 mins as compared to the standard at 3.49 ± 0.03 (Figure 1).

Method development

The chromatographic methods reported in literature and in official books are tedious, costly and the reported retention times are also high[12]. The sodium-1- octanesulfonate is used as ion pairing agent, which helps in early elution of Loperamide Hydrochloride. The method is validated in terms of linearity, specificity, accuracy, precision and limit of detection (LOD) and limit of quantification (LOQ) according to ICH guidelines.

Linearity[11]

The linearity of Loperamide Hydrochloride was found to obey the Beer's law in the concentration range of 1 -5 µg/ml. The coefficient of correlation was found to be 0.9995 ± 0.0002.

Specificity[13, 14]

Specificity of the method was determined by interference study of excipients and interpreted in terms of the change in retention time,

no. of theoretical plates and tailing factor of the chromatogram. There were no changes in the retention time of the chromatogram of Loperamide hydrochloride. There was no marked difference found in no. of theoretical plates and tailing factor in presence of excipients. So it can be concluded the method is specific for Loperamide hydrochloride.

Accuracy[15, 16]

To ascertain the accuracy of the proposed methods, recovery studies were carried out by standard addition method at three different levels (80%, 100% & 120%). The results of recovery studies, expressed as percent recovery, were satisfactory and are presented in Table No.4.

Precision[17, 18]

The reproducibility of the proposed method was determined by analyzing tablets at different time intervals on same day in triplicates (Intra-day assay precision) and on three different days (Inter-day assay precision) (Table 5).

For the in vitro dissolution study different media were tried[19]. With reference to the reference methods in official book, 0.1% sodium lauryl sulfate in 0.1N hydrochloric acid gave the best release rate of Loperamide hydrochloride. The release is listed in Table 6 and interpreted in terms of relative standard deviation. R.S.D. value below 2 (± 0.635) indicates the suitability of the developed method in in-vitro evaluation of the combined dosage form of Loperamide hydrochloride.

Table 4: Recovery Study by Standard Addition Method

Level of recovery	Amount of sample taken (µg/ml)	Amount of standard added (µg/ml)	Percent recovery (Mean* ± R.S.D)
80%	2	1.6	98.2 ± 0.305
100%	2	2	
120%	2	2.4	

*Mean of six determinations

Table 5: Precision of the method

Label claim of the formulation (mg)	Intra-day precision Mean* ± R.S.D	Inter-day precision Mean# ± R.S.D
2	100.5±0.55	99.78±0.63

*Mean of six formulations at a constant concentration level in triplicate on the same day

Mean of six formulations at a constant concentration level on three consecutive days

The Limit of Detection (LOD) and Limit of Quantification (LOQ) were found to be 0.012 µg/ml and 0.37 µg/ml respectively.

Table 6: In-vitro release of Loperamide hydrochloride of F1

Trial no. of the formulation F1	Label claim (mg)	Drug release (Mean*) (%)	Mean*±R.S.D.
T1	2	95.2	
T2	2	95.8	96. 0 ± 0.635
T3	2	95.4	
T4	2	96.5	
T5	2	96.8	
T6	2	96.3	

*Mean of six determinations

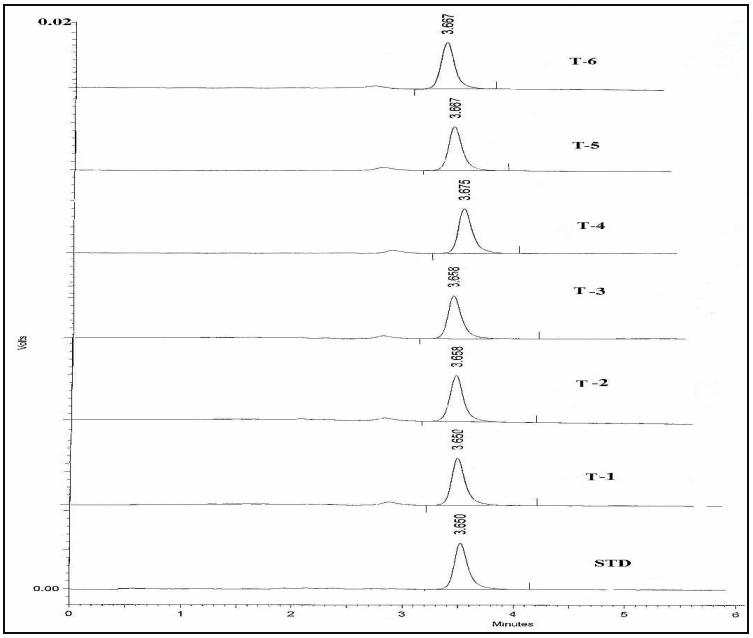

Fig. 2: Dissolution profile of F1 formulation

CONCLUSION

Loperamide hydrochloride Chewable tablets were prepared by wet granulation technique. Use of simethicone to dry powder blend improve hardness and provides good physical appearance to the tablets. Addition of Loperamide hydrochloride to binder solution and using proper amount of surfactant (SLS) to blend increase content uniformity and better dissolution of Loperamide hydrochloride. The developed chromatographic method is easier and cost effective than the other reported and official methods. The validation data indicates the suitability of the developed chromatographic method for quantitative and quality assurance of Loperamide hydrochloride in small scale laboratories.

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