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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF BUCCAL TABLETS OF LORATADINE FOR EFFECTIVE TREATMENT OF ALLERGY

Borgaonkar PA*, Virsen TG, Hariprasanna RC and Najmuddin M

Department of Pharmaceutics, RMES'S College of Pharmacy, Gulbarga, Karnataka, India.

*Corresponding Author: prashant7522@gmail.com

ABSTRACT

Mucoadhesive buccal tablets of Loratadine were prepared with an objective of enhancing the bioavailability by minimizing first pass metabolism. The buccal tablet were prepared by using HPMC K4M as primary polymer alone and in combination with secondary polymers like Chitosan, Sodium alginate in varying concentration by direct compression method. Estimation of Loratadine was carried out spectrophotometrically at 248 nm. The tablets were evaluated for hardness, thickness, weight variation, friability, drug content, surface pH, swelling index, *in vitro* drug release, mucoadhesive strength and also the effect of secondary polymer concentration on these parameters was studied. Short-term stability studies (40±2° C/ 75±5% RH for 3 months) indicated that the buccal tablets are stable with respect to drug content and dissolution. FTIR spectroscopic studies indicated that there are no drug-excipient interactions. All the tablets showed good mucoadhesive strength of 4.00 to 7.00 gm and force of adhesion increased with increase in polymer concentration and drug release reduced consequently. The surface pH of the tablet was in the range of 6.7 to 6.9 which does not irritate mucosa. The formulations HP1 (containing 30% HPMC K4M) was found to be promising, which showed $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values of 3.20 h, 5.48h, 7.16 h and drug released 99.00% within 8 h respectively. These formulations have displayed good bioadhesion strength (4.0 gm).

Keywords: Loratadine, HPMC K4M, Sodium alginate, Chitosan.

INTRODUCTION

The interest in novel routes of drug administration is to increase the therapeutic efficacy of the drug. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. This route has been used successfully for the systemic delivery of number of drug candidates. Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is an alternative route to administer drugs to patients who are unable to be dosed orally. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets, adhesive gels, and adhesive patches [1].

Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and depending on the particular

drug, a better enzymatic flora for drug absorption [2].

The strategy for designing buccoadhesives is based principally on the utilization of polymers with suitable physicochemical properties, such as polyacrylic acid (carbomer [CB]) and cellulose derivatives (hydroxypropylmethylcellulose [HPMC]) [3].

Loratadine is tri-cyclic antihistamine, which selectively antagonizes peripheral histamine H_1 receptor. Loratadine undergoes extensive first-pass hepatic metabolism and has 40% bioavailability, its half life is 8 hours [4]. Therefore, a buccal tablet of Loratadine will be formulated to prevent first-pass metabolism and to improve therapeutic efficacy.

MATERIALS AND METHODS

Loratadine was gift sample from Cadila Pvt. Ltd. Ahemadabad. All other reagents and chemicals used were of analytical grade.

Preparation of buccal tablets of Loratadine by direct compression method

Direct compression method was employed to prepare buccal tablets of Loratadine using HPMC K4M, Chitosan, Sodium alginate as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula and were passed through #40 to get uniform particle size. The drug and all the ingredients except lubricants were taken on a butter paper with the help of a stainless steel spatula and the ingredients were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was compressed by using 7mm punch on a single stroke tablet punching machine (Rimek, minipress rotary machine, Karnavathi engineering ltd, Gujarat.)

Evaluation of mucoadhesive buccal tablets of Loratadine

1) Hardness test [5, 6]

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

2) Thickness [5, 7]

The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge.

3) Friability test [5, 8]

The friability of tablet was determined by using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions in which tablet droped from 6 inch distance. The tablets were dusted weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

4) Uniformity of weight [5, 8]

The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The individual weight was compared with average weight for determination of percent deviation.

5) Uniformity of drug content [9]

Five tablets were powdered in a glass mortar and the powder equivalent to 10 mg of drug was placed in a stoppered 10 ml conical flask. The drug was extracted with 60% methanol with vigorous shaking and filtered into 10 ml volumetric flask. Further appropriate dilution were made by using phosphate buffer pH 6.8 to make 10 mcg/ml concentration and absorbance was measured at 248 nm against blank (phosphate buffer pH 6.8).

6) Surface pH study [10]

A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of phosphate buffer pH 6.8 for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min.

7) Swelling Index [10]

The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8 The initial weight of the tablet was determined and then tablet was placed in 15 ml phosphate buffer pH 6.8 in a petridish and then was incubated at 37 ± 1° C. The tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h) blotted with filter paper and reweighed (W_2). The swelling index is calculated by the formula:

$$\text{Swelling index} = 100 (W_2-W_1) / W_1.$$

Where, W_1 = Initial weight of the tablet.

W_2 = Final weight of tablet.

8) Mucoadhesion strength [11]

Prior to the study approval was obtained from Institutional Animal Ethics Committee (Reg. No.-341/CPCSEA). Mucoadhesion strength of the tablet was measured on a modified physical balance (Figure 1.) employing the method as described by Gupta *et al* using sheep buccal mucosa as model mucosal membrane. Fresh sheep buccal mucosa was obtained from a local slaughter house and was used within 2 h of slaughtering. The mucosal membrane was washed with distilled water and then with phosphate buffer pH 6.8. A double beam physical balance was taken and to the left arm of balance a thick thread of suitable length was hanged and to the bottom side of thread a glass stopper with uniform surface was tied. The buccal mucosa was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker which was placed in a 500 ml beaker filled with phosphate buffer pH 6.8 kept at 37° C such that the buffer reaches the surface of mucosal membrane and keeps it moist. The buccal tablet was then stuck to glass stopper from one side membrane using an adhesive (Feviquick).

The two sides of the balance were made equal before the study, by keeping a weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the glass stopper along with the tablet over the mucosal membrane with a weight of 5 g. The balance was kept in this position for 3 min. Then, the weights were increased on the right pan until tablet just separated from mucosal membrane. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with phosphate buffer and left for 5 minutes before placing a new tablet to get appropriate results for the formulation.

Figure 1: Bioadhesion testing apparatus

***9) In vitro* drug release study** [8]

The study was carried out in USP XXIII tablet dissolution test apparatus-II (Campbell electronics, DR-6 Dissolution Appratus), employing paddle stirrer at 50 rpm and 900 ml of phosphate buffer pH 6.8 with 0.5% Tween 80 as dissolution medium maintained at 37±0.5 °C. At different time interval 5 ml of sample was withdrawn and replaced with fresh medium. The samples were filtered through 0.25 µm membrane filter paper and analyzed for Loratadine after appropriate dilution at 248 nm using PG instrument T_{80} model UV-Visible spectrophotometer.

The results of *in vitro* release profiles obtained for the formulations were fitted into four models of data treatment as follows :

1. Cumulative percent drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining versus time (first- order kinetic model).
3. Cumulative percent drug released versus square root of time (higuchi's model).
4. Log cumulative percent drug released versus log time (korsmeyer - Peppas equation).

10) Short Term Stability studies [12]

Short- term stability study was performed at a temperature of 40 ±2° C over a period of three

months (90 days) on the promising buccal tablets of Loratadine. Sufficient numbers of tablets (10) were individually wrapped using aluminium foil and packed in amber colour screw cap bottle and kept in stability chamber for 3 months. Samples were taken at each month interval for evaluation of drug content and *in vitro* drug release study.

11) Polymer drug interaction study [12]

The drug-polymer and polymer-polymer interaction was studied by FTIR spectrometer using Shimadzu 8400-S, Japan.

RESULT

Table 1: Composition of Buccal Tablet of Loratadine.

Ingredients mg/tablet	Formulation code								
	HP1	HP2	HP3	HC1	HC2	HC3	HS1	HS2	HS3
Loratadine	10	10	10	10	10	10	10	10	10
HPMC K4M	30	40	50	50	50	50	50	50	50
Chitosan	--	--	--	5	10	15	--	--	--
Sodium Alginate	--	--	--	--	--	--	5	10	15
Mannitol	38.8	28.8	18.8	13.8	8.8	3.8	13.8	8.8	3.8
MCC	20	20	20	20	20	20	20	20	20
Mg. Stearate	1	1	1	1	1	1	1	1	1
Sodium saccharine	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total	100	100	100	100	100	100	100	100	100

Table 2: Physicochemical Properties of Buccal Tablets

Formulation code	Hardness Kg/cm^2*	Thickness (mm)*	Friability (%)*	Weight Variation of Tablet (mg) *	Drug Content (%)*
HP1	5.4±0.06	3.20±0.06	0.55±0.00	98±0.99	97.41±0.34
HP2	5.5±0.03	3.25±0.06	0.51±0.01	100±0.38	98.23±0.38
HP3	5.6±0.02	3.29±0.00	0.87±0.03	101±0.99	100±0.88
HC1	5±0.05	3.23±0.06	0.50±0.00	98±0.99	100±0.56
HC2	4.5±0.02	3.26±0.06	0.32±0.02	98±0.38	98.70±0.33
HC3	4±0.07	3.33±0.00	0.75±0.01	99±0.99	96.98±0.84
HS1	6±0.04	3.21±0.06	0.20±0.02	101±0.17	97.84±0.41
HS2	5±0.08	3.25±0.01	0.66±0.01	99±0.40	97.41±0.54
HS3	4.5±0.03	3.31±0.00	0.41±0.01	99±0.20	98.70±0.58

*Average of three determinations.

Table 3: Result of Surface pH, Swelling Index and Mucoadhesive Strength of all Formulations

Formulation code	Surface pH*	Swelling Index After 8 hr	Mucoadhesive Strength
HP1	6.9±0.17	22.06	4.000
HP2	6.8±0.12	27.73	4.900
HP3	6.7±0.11	31.80	6.350
HC1	6.9±0.17	16.01	6.500
HC2	6.9±0.23	20.86	6.550
HC3	6.8±0.32	25.61	6.700
HS1	6.8±0.07	18.21	6.400
HS2	6.7±0.02	21.76	6.900
HS3	6.6±0.06	27.20	7.000

*Average of three determinations,

Table 4: In Vitro Drug Release Parameters

Formulation code	$t_{50\%}$ (h)	$t_{70\%}$ (h)	$t_{90\%}$ (h)	Cumulative % drug release in 8 hrs
HP1	3.20	5.48	7.16	99.00
HP2	4.18	6.03	7.53	91.23
HP3	5.00	6.26	>8.00	85.45
HC1	4.13	6.05	>8.00	83.80
HC2	5.00	6.24	>8.00	82.15
HC3	5.30	7.05	>8.00	77.61
HS1	4.46	6.26	>8.00	82.56
HS2	5.33	7.18	>8.00	75.96
HS3	5.54	7.58	>8.00	70.18

Table 5: Kinetic Data of Formulations of Mucoadhesive Tablets

Formulation Code	r	Zero Order	First Order	Higuchi equation	Peppas equation
HP1	r	0.9876	-0.1945	0.9707	0.7556
HP2	r	0.9896	-0.1628	0.9652	0.7609
HP3	r	0.9919	-0.0736	0.9645	0.7781
HC1	r	0.9955	-0.1236	0.9635	0.8570
HC2	r	0.9963	-0.0721	0.8991	0.8662
HC3	r	0.9954	0.0183	0.9497	0.8858
HS1	r	0.9983	-0.0676	0.9625	0.8758
HS2	r	0.9951	0.0294	0.9433	0.8802
HS3	r	0.9932	0.0645	0.9360	0.9111

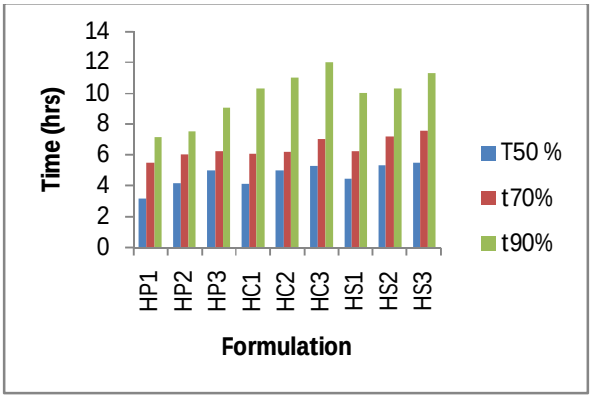

Figure 2: Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of buccal tablets of Loratadine.

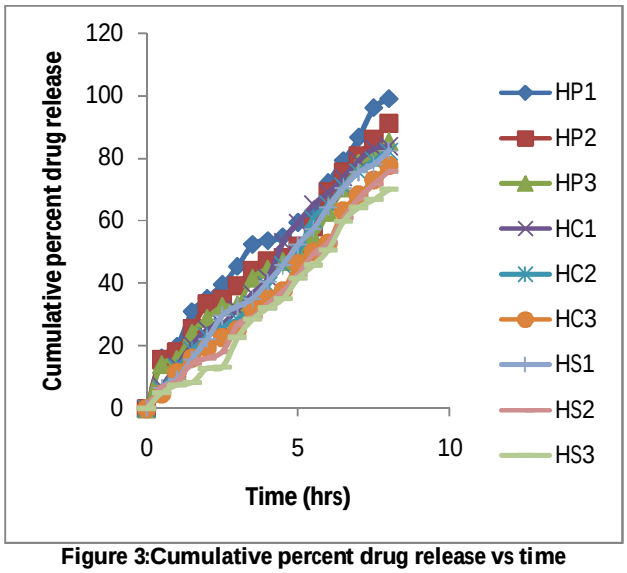

Figure 3:Cumulative percent drug release vs time

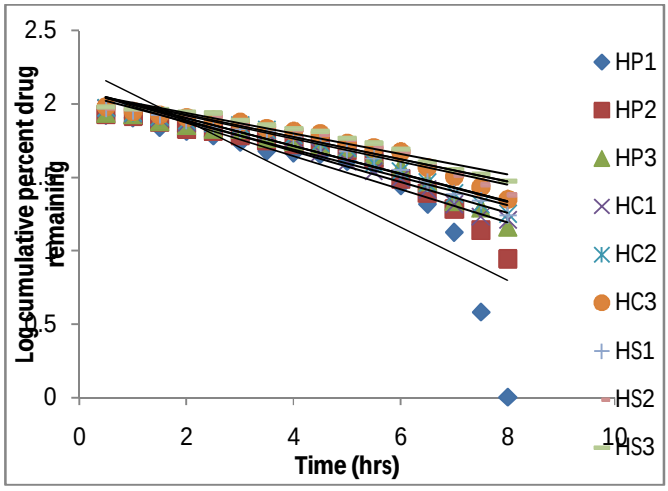

Figure 4.: Log cumulative percent drug remaining vs time plots (first order)

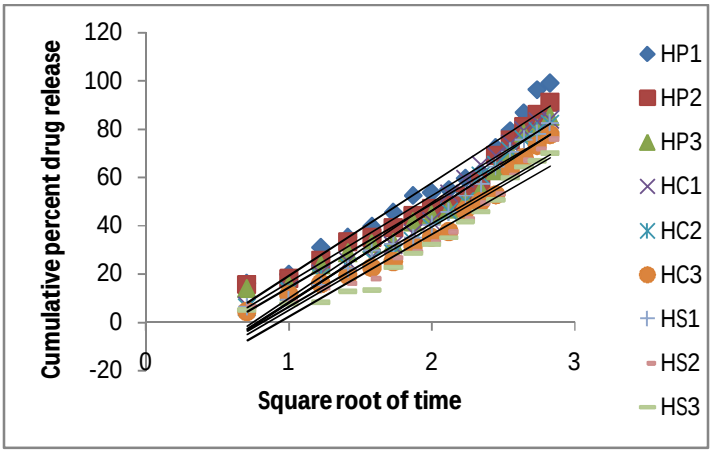

Figure 5: Cumulative percent drug released vs square root of time plots (Higuchi plots)

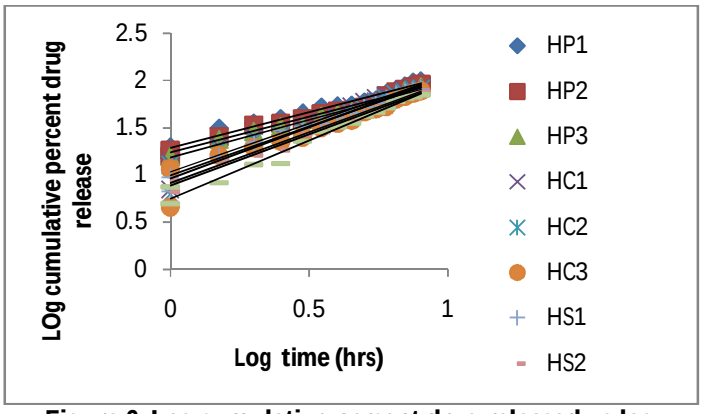

Figure 6: Log cumulative percent drug released vs log Time plots (Peppas plots)

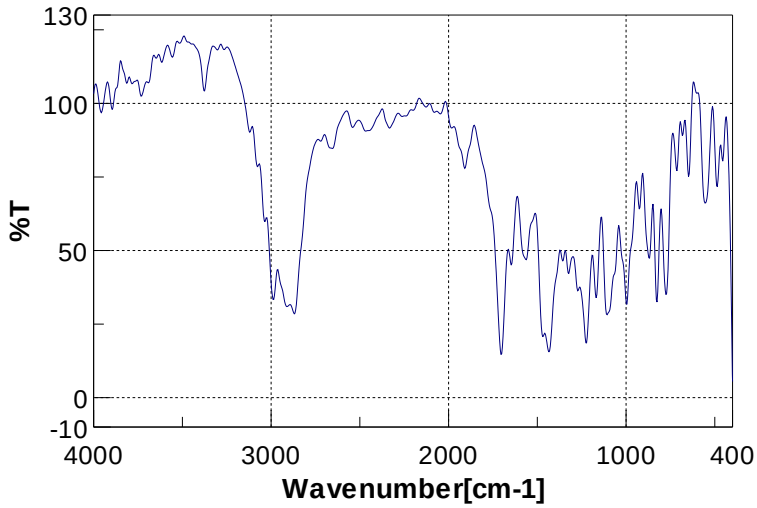

Figure 7: IR spectrum of Loratadine

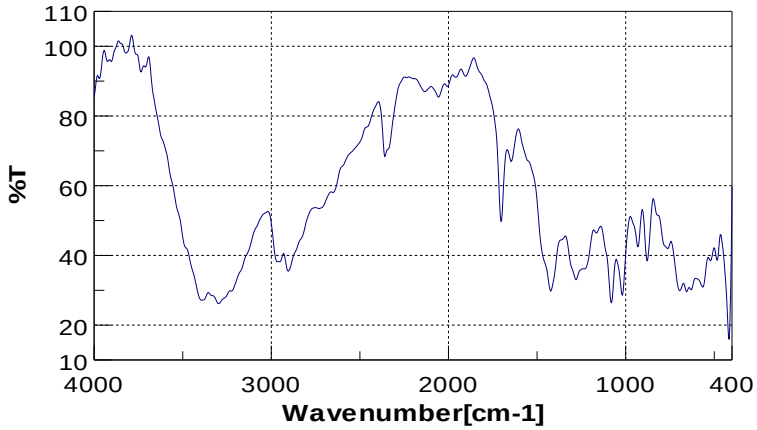

Figure 8: IR spectrum of HP1

DISCUSSION

It could be observed that all the prepared tablets fulfil the the requirements of buccal tablets. The hardness of prepared buccal tablets was found to be in the range of 4.00 to 6.00 kg/cm^2 and shown in Table-2. The thickness and weight variation were found to be uniform as indicated by the low values of standard deviation. The thickness and weight of the prepared buccal tablet were found to be in the range of 3.20 to 3.33 mm and 98 to 101 mg respectively. Friability values of all tablets were less than 1 % indicate good mechanical strength to with stand the rigorous of handling and transportation. The average drug content of the buccal tablets was found to be within the range of 96.98 to 100 %.

The surface pH of all the formulations was found to be in the range of 6.7 to 6.9, hence formulations do not cause any irritation in the oral cavity. The swelling indices of the tablets increased with increasing amount of HPMC K4M but extend of swelling decreases with addition of secondary polymers like Chitosan and Sodium alginate Table-3. The mucoadhesivity of tablets was found to be maximum in case of formulation HS3 i.e. 7.00 gm. The results are given in Table-3.

In vitro drug release data of the all the buccal tablet formulations of Loratadine was subjected to goodness-of-fit test by linear regration analysis according to zero order, first order kinetics, Higuchi's and Korsmeyer-Peppas equations to assertion mechanism of drug release. It is evident that all the formulations displayed zero order release kinetics ('r' values from 0.9876 to 0.9963). Higuchi and Peppas data reveals that the drug released by Non-Fickian diffusion mechanism Table-5. The *in vitro* release parameter values ($t_{50\%}$, $t_{70\%}$, and $t_{90\%}$) displayed by the various formulations range from 3.20 h to 5.54 h ($t_{50\%}$), 5.48 h to 7.58 h ($t_{70\%}$) and 7.16h to 12 h ($t_{90\%}$). The formulations HP1 (30 % HPMC K4M) shows drug release 99% within 8 h, further increase in concentration of polymer resulted in decrease drug release, this can be attributed to the excellent swelling property of HPMC K4M. The $t_{50\%}$, $t_{70\%}$, and $t_{90\%}$ was 3.20 h, 5.48 h, 7.16 h respectively and mucoadhesive strength is 4.00 gm. The FTIR studies revealed that there was no physicochemical interaction between Loratadine and HPMC K4M and other excipient.

CONCLUSION

It can be concluded that the buccal tablets of Loratadine can be prepared by using natural polymers to control the drug release and also to avoid the first pass metabolism. The formulations HP1 was found to be promising, which shows an *in vitro* drug release of 99% in 8 h along with satisfactory mucoadhesion strength i.e 4.00 gm and $t_{50\%}$, $t_{70\%}$, and $t_{90\%}$ was 3.20, 5.48, 7.16 respectively.

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