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Original Article

Formulation and evaluation of taste masked Amlodipine Besylate Fast-dissolving Sublingual Tablets

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Keywords: Amlodipine Besylate (AML), drug polymer complex (DPC), sublingual tablet (SLT), Eudragit EPO, sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CPV), direct compression, sodium carboxymethyl cellulose (SCMC), hot melt extrusion

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ABSTRACT:

Aim: In the present study was to taste mask the Amlodipine Besylate (AML) by forming complex with Eudragit EPO by and further to enhance the dissolution rate AML by formulating these drug polymer complex (DPC) into fast dissolving sublingual tablet (SLT) by direct compression technique. **Objectives:** To prepare DPC by hot melt extrusion method. Physico-chemical characterization of DPC by FT-IR, DSC and XRD studies. To check the superiority of selected superdisintegrants [sodium starch glycolate (SSG), croscarmellose sodium (CCS), crosspovidone (CPV) and sodium carboxymethyl cellulose (SCMC)] in enhancing the dissolution rate of AML from its SLT. To fasten the onset of action, to decrease the hepatic metabolism and thereby increasing AML's bioavailability in comparison to its conventional tablets. **Methods:** Standard calibration curve of AML in pH 6.8 phosphate buffer was constructed by spectrophotometric method, drug-excipient compatibility was checked by FT-IR studies. All the Formulations were evaluated for pre- & post-compression studies. Accelerated stability studies up to 3 months were conducted for the optimized formulation in a HDPE container pack, as per ICH guidelines. **Results and Discussions:** Superdisintegrants used in the study are compatible with AML. Pre- & post- compression parameters were within the acceptable limits for all formulations. *In vitro* dissolution kinetic studies indicate the release of AML from SLT increases with the increased concentration of superdisintegrants. The order of superdisintegrants in enhancing the dissolution rate of AML is CPV > SCMC > CCS > SSG. Formulation F3 with 8% w/w CPV, had the highest dissolution efficiency at 10 min (DE_{10} = 49.80 %); first order dissolution rate constant (K_1 = 0.198 min^{-1}) with a regression coefficient (r^2 = 0. 956) and lesser time for 50% of drug release (t_{50} < 6 min), which shows min wetting time of 21.12 sec and min disintegration time of 17 sec, was considered as the optimal SLT. It passed the test for stability as per ICH guidelines. **Conclusion:** An optimized taste masked AML SLT with the taste masked DPC in combination with the addition of artificial flavor and sweetener was formulated by the direct compression technique, with 8% w/w CPV as superdisintegrant, which will fasten the onset of action and enhances the bioavailability of AML in comparison to its conventional tablets.

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INTRODUCTION

The oral route is the most preferred route of administration of dosage forms, due to its potential advantages like ease of administration, convenient dosing, self-medication, no pain and patient compliance. Hence tablets and capsules are the most popular dosage forms [1], but the important drawback of these dosage forms is dysplasia [2] which can be solved by developing a novel drug delivery system (NDDS); fast dissolving sublingual tablet (SLT). The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first- pass metabolic processes. A fast dissolving tablet system can be defined as a dosage form for oral administration, which, when placed in the mouth, rapidly dispersed or dissolved and can be swallowed in the form of liquid. For these formulations, the small volume of saliva is usually sufficient to result in disintegration in the oral cavity.

The drug can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract [3- 5].

AML is used for treating high blood pressure, certain types of angina, and coronary heart failure. It is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the trans- membrane influx of calcium ions into vascular smooth muscle and cardiac muscle [6]. It is a crystalline powder with a molecular weight of 567.1 gm/Mol. It is slightly soluble in water. Its absolute bioavailability has been estimated to be between 64% and 80% only, due to its extensive hepatic metabolism, when taken as a conventional tablet, hence it is a suitable candidate for to formulate as SLT. The intense bitter taste of the AML is masked by preparing DPC with Eudragit EPO in 1:1 ratio by hot melt extrusion method.

The purpose of this investigation was to formulate these taste masked DPC into SLT by direct compression technique. The present study was also aimed to optimize the type and concentration of superdisintegrant among SSG, CPV, CCS and SCMC.

MATERIALS AND METHODS

Materials: Amlodipine Besylate was obtained from Hetero Drugs Pvt Ltd, Hyderabad, India as a gift sample, powder vanilla flavor was a gift sample from Firmenich, Chennai, Eudragit EPO, sodium starch glycolate (Primogel®), croscarmellose sodium (Ac-Di-Sol®), crospovidone (Crosspovidon M®), carboxymethyl cellulose sodium (Avicel® CL-611), mannitol (Pearlitol® 200SD), Aspartame, magnesium stearate and colloidal SiO_2 (Aerosil® 200) were procured from S.D. Fine Chem. Pvt. Ltd., Mumbai. All the excipients used in the study were of pharmaceutical grade.

Methods:

The Standard calibration curve of AML in pH 6.8 phosphate buffer [7]**:**

Preparation of pH 6.8 phosphate buffer: Place 50 ml of 0.2M potassium hydrogen phosphate in a 200ml volumetric flask, add the 22.4 ml of 0.2 M sodium hydroxide and the add water to the volume.

Preparation of stock solution-I: Stock solution-I (1mg/mL) was prepared by dissolving 50 mg of AML in 10 mL of methanol in a 50mL volumetric flask and the volume was made up to mark with pH 6.8 phosphate buffer.

Preparation of stock solution-II: Stock solution-II (100 µg/mL) was prepared by taking 10 mL of stock solution-I into a 100mL volumetric flask and the volume was made up to mark with pH 6.8 phosphate buffer.

Procedure: Aliquots of (0.2, 0.4, 0.6, 0.8 and 1.0 mL) of Stock solution-II was transferred into a series of 10 mL volumetric flasks and the volume was made up to mark with pH 6.8 phosphate buffer to obtain concentrations of (2, 4, 6, 8 and 10 µg/mL). The obtained concentrations were analysed at the λ_{max} 366 nm using a UV-Visible spectrophotometer (UV-1700, Shimadzu, Mumbai, India) and their absorbance were noted. The Standard calibration curve was plotted by taking the concentration of drug solution (µg/mL) on X-axis and absorbance on Y-axis. (**Fig. 1**).

Preparation of Drug Polymer Complexes (DPC) for taste masking [8]: (1:1) ratio of AML: Eudragit EPO taste masked complexes were prepared by hot melt extrusion method to mask the bitter taste of AML. Eudragit EPO is melted at 100°C, #60 sieve passed AML is incorporated slowly with stirring to obtain a uniform mixture. The mixture is cooled to room temperature, coarsely ground and passed through #60 sieve to obtain a fine powder.

Physicochemical characterization of DPC [8]**:** FT-IR spectra, DSC thermograms and X-ray diffractograms were recorded for pure AML and (1:1) ratio of AML: Eudragit EPO DPC.

FT-IR: Spectra were recorded by an IR spectrophotometer (Shimadzu, FTIR 8700), in the region between 400 and 4000 cm^{-1} by the direct sampling method.

Differential Scanning Calorimetry (DSC): DSC thermographs were recorded using a differential scanning calorimeter (DSC-1, Star System, Metllar Toledo). The apparatus was calibrated with purified indium (99.9%). (2 mg) samples were placed in flat-bottomed aluminium pan and heated at a constant rate of 10 °C/min, in an atmosphere of nitrogen in a temperature range of 40–400°C.

X- Ray Diffractometry (XRD): The X-ray diffractograms were recorded using Philips diffractometer (PW 1140) and CuKa radiation; voltage, 40 kV; current, 20 mA. Diffractogram was run at a scanning speed of 2°/min over

Drug-excipient compatibility (FT-IR) studies [8]**:** Were performed on AML and (1:1 ratio) physical mixtures of AML with superdisintegrants by an IR spectrophotometer (Shimadzu, FTIR 8700), in the region between 400 and 4000 cm^{-1} by the direct sampling method.

Preparation of AML SLT [8]**:** All the formulations were prepared by direct compression method, by keeping the amount of AML constant at 10 mg which is taken as taste masked (1:1) DPC. The composition of other excipients is varied as mentioned in formulation table (**Table 1**). In these formulations CPV, CCS, SSG and SCMC are used as superdisintegrants, mannitol as a directly compressible diluent, aspartame is an artificial sweetener, powder vanilla flavor as a flavoring agent, magnesium stearate as a lubricant, colloidal SiO_2 as glidant. DPC and all the other excipients excluding magnesium stearate and colloidal SiO_2 were co-sifted through Sieve No. # 40 (ASTM), blended uniformly in a poly bag for 10 min and lubricated with Sieve No. # 60 (ASTM) passed magnesium stearate and colloidal SiO_2 and mixed in a poly bag for an additional 2-3 min.

Tablets were compressed on a tablet compression machine (10 station, Yogesh Pharma Machinery Pvt. Ltd., India) fitted with 8 mm standard round punches with an Avg. wt. of 150 mg and hardness of 3- 4 kg/cm^2.

Table 1: Formulation table of AML SLT

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
(1:1) DPC	20	20	20	20	20	20	20	20	20	20	20	20
CPV	6	9	12	-	-	-	-	-	-	-	-	-
CCS	-	-	-	6	9	12	-	-	-	-	-	-
SSG	-	-	-	-	-	-	6	9	12	-	-	-
SCMC	-	-	-	-	-	-	-	-	-	6	9	12
Aspartame	6	6	6	6	6	6	6	6	6	6	6	6
P. Vanilla flavor	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg. Stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Colloidal SiO_2	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Mannitol	112	109	106	112	109	106	112	109	106	112	109	106
Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

*Quantity of ingredients per each tablet was expressed in mg; total wt. of the tablet is 150 mg.

Precompression Studies [9]**:** The directly compressible AML SLT blends were evaluated for their flow properties.

Angle of Repose (θ): Was determined by funnelling method, the blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The blend was poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. The θ is calculated by the equation.

$$\theta = \tan^{-1} h / r \quad \text{..... Eq. No. (1)}$$

Where, θ = angle of repose, h = height of the heap and r = radius of base of heap circle.

Density:

Bulk density (BD): A quantity of 2 gm of SLT blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10mL measuring cylinder and the volume is noted as bulk volume. The BD was calculated by the equation.

Bulk density (BD) = weight of powder/ Bulk volume ……. Eq. No. (2)

Tapped density (TD): After the determination of BD, the measuring cylinder was fitted to a tapped density apparatus. The tapped volume was measured by tapping the powder for 500 times. Later the tapping was done for another 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for another 1250 times and the constant tapped volume was noted. The TD was calculated by the equation.

Tapped density (TD) = Wt. of powder / Tapped volume ……. Eq. No. (3)

Carr's Index (CI): The percentage of CI is calculated by the equation.

Carr's index (CI) = (TD-BD) ×100 / TD ……. Eq. No. (4)

Hausner's Ratio (HR): Is a number that correlates to the flow ability of a powder. It is calculated by the equation.

Hausner's Ratio (HR) = TD /BD ……. Eq. No. (5)

Precompression studies of all the formulations were carried out in triplicate (n = 3); the consolidated results (mean ± SD) were tabulated in (Table 2).

Post compression studies [9]**:**

Avg. wt. of tablets: An electronic balance (Mettler Toledo, 3-MS-S / MS-L, Japan) was used to accurately weigh the individual wt. of twenty tablets which were randomly selected from each formulation and checked for the acceptability of wt. variation.

Friability test: The friability of the 20 tablets from each batch (n=1) was tested by a fribilator (SINGLA, TAR 120, Germany) at a speed of 25 rpm for 4 min. The tablets were then dedusted, reweighed, and percentage weight loss was calculated by the equation,

% Friability = (Initial Wt.- Wt. after friability) × 100 / Initial Wt. ……... Eq. No. (6)

Hardness test: To evaluate the diametrical crushing strength, 3 tablets from each formulation were tested using a hardness tester (Monsanto type hardness tester, MHT-20, Campbell Electronics, India).

Thickness: Thickness of 3 tablets from each formulation was determined using a Vernier caliper (Mitutoyo Corporation, Japan).

In vitro disintegration time & fineness of dispersion [10]**:** It is specified in the European Pharmacopeia (EP 6.0), the disintegration time determination procedure for fast disintegrating tablets is same as that of conventional uncoated tablets and the tablets should be dispersed within less than 3 min. The obtained tablet's dispersion was passed through a sieve screen with a nominal mesh aperture of 710 mm to confirm the fineness of dispersion.

Wetting time and Swelling Index [11]**:** A piece of tissue paper folded twice was placed in petri dish having an internal diameter of 5.5 cm, containing 6 mL of water. A tablet was placed on the paper and the time required for complete wetting was measured as wetting time (WT), using a stopwatch. The wetted tablet was then reweighed and swelling index (SI) was determined using the following equation.

Swelling Index (SI) = [($W_a - W_b$) / W_b] × 100 …… Eq. No. (7)

Where, W_b and W_a were the weights of the tablet before and after swelling.

Assay [8]**:** To evaluate the drug assay, 3 tablets from each formulation were powdered in mortar and pestle. Blend equivalent to 1 mg of AML was accurately weighed and transferred into a 100 mL volumetric flask containing 10 mL of methanol, and the volume was made up to 100 mL with pH 6.8 phosphate buffer and ultra-sonicated for 2 min to extract the AML from the tablet blend and filtered through 0.45 µm poly tetra fluoro ethylene (PTFE) filter disc. The filtrate was suitably diluted if necessary and its absorbance was measured by UV-Visible spectrophotometer at 366 nm.

Post compression studies of all the formulations, except for Avg. wt. and friability test was carried out in triplicate (n = 3); the consolidated results as, (mean ± SD) were tabulated in (**Table 3**).

In vitro dissolution studies [8]**:** Were performed with 10 mg of pure AML, DPC equivalent to 10 mg of AML and 3 tablets from each batch using the dissolution apparatus (Lab India Disso 2000, Lab India Analytical Instruments Pvt Ltd, India) with USP-II / Paddle**.** Each dissolution flask contains 900 mL of pH 6.8 Phosphate buffer; the speed of the paddle was maintained at 50 rpm; the temperature was kept stable at 37 ^{0}C ± 0.5 ^{0}C. At required time intervals, 5 mL of dissolution media was withdrawn with a pipette containing 0.45 µ (PTFE) filter disc, suitably diluted if necessary and its absorbance was measured by UV-Visible spectrophotometer at 366 nm. Furthermore, 5 mL of fresh pH 6.8 phosphate buffer was replaced to the dissolution flask to keep the volume of dissolution medium constant. The dissolution profiles were represented graphically in **Fig. 5 & 6**.

In vitro dissolution kinetics [11]. The *in vitro* drug release data was fitted into zero-order plots/ dissolution profiles (cum. % drug dissolved *Vs* time) and first order plots (log % drug undissolved *Vs* time) as per the following equations.

Zero order: $Q_t = Q_0 + K_0t$…….. Eq. No. (8)

First order: log Q_t = log Q_0–K_1t / 2.303…… Eq. No. (9)

Where *Qt* is the amount of the drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution, K_0 & K_1 refers to the rate constants of zero & first order respectively.

Dissolution Efficiency at 10 min (DE_{10}) by Trapezoid Rule [12]; and time for 50 % drug release (t_{50}) were calculated from dissolution profiles.

Equations for calculating DE_{10}:

$[AUC]_{t1}^{t2} = \frac{1}{2}(C_1+C_2)(t_2-t_1)$ …….. ***Eq. No. (10)***

$[AUC]_0^{10} = [AUC]_0^2 + [AUC]_2^4 + [AUC]_4^6 + [AUC]_6^8 + [AUC]_8^{10}$ ***Eq. No. (11)***

$DE_{10} = \frac{[AUC]_0^{10}}{Total\ area\ at\ 10\ min} X\ 100$ …… ***Eq. No. (12)***

Where, $[AUC]_{t1}^{t2}$= Area under curve between time points t_1 to t_2

Total area at 10 min = 10 X 100 = 1000 cm^2

First order dissolution rate constant (K_1) and regression coefficient (r^2) of first order profiles were calculated from first order plots. The consolidated *in vitro* dissolution kinetic parameters of AML SLT were tabulated in **Table 4**.

Accelerated stability studies of the optimized AML SLT; F3 [13]**:** Were carried according to an international conference on harmonization (ICH) guidelines. 20 tablets were packed in each 10 CC HDPE bottle and sealed thermally and were placed in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45 °C ± 2 °C and 75 % ± 5 % RH. Up to 3 months, at the end of every month the respective samples were withdrawn and evaluated for post compression studies.

The consolidated results of post compression studies on accelerated stability samples of optimized formulation F3; except Avg. wt. and friability test, the other was carried out in triplicate (n = 3) and the results as (mean ± SD) were tabulated in (Table 5).

In vitro dissolution profiles of initial and accelerated stability samples of optimized AML SLT; F3 were represented graphically in **Fig. 7**.

RESULTS AND DISCUSSION

The standard calibration curve of AML in pH 6.8 phosphate buffer: Based on the measurement of absorbance at λ_{max} of 366 nm in pH 6.8 phosphate buffer in the conc. range of 0 -10 µg/ml, a straight line with an equation, y = 0.0266 x + 0.0009 and a regression coefficient (r^2) of 0.999 was obtained, which indicates it follows the Beers-Lambert law in the mentioned concentration range (**Fig. 1**).

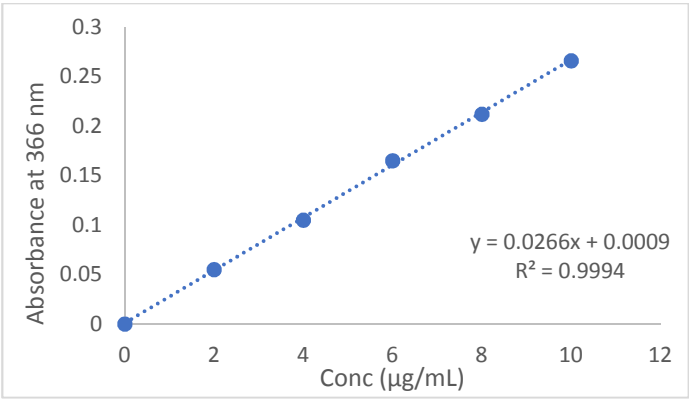

Fig. 1: Standard calibration curve of AML in pH 6.8 phosphate buffer at 366 nm.

Physicochemical characterization of DPC

FT-IR studies: The FT-IR spectra of AML and (1:1 ratio) AML: Eudragit EPO DPC is depicted in **Fig. 2A & B**. The FT-IR spectrum of AML is characterized by sharp characteristic peaks at 3300.20, 3158.50, 1651.08, and 1616.08 cm^{-1}.

All the above characteristic peaks appear in the (1:1 ratio) AML: Eudragit EPO DPC at same wavenumber indicating no modification or interaction with the drug in DPC [14].

Differential scanning calorimetry (DSC) studies: The DSC spectra of AML and (1:1 ratio) AML: Eudragit EPO DPC is depicted in **Fig. 2C & D**. The DSC thermogram of pure AML was of a typical crystalline substance, exhibits a sharp endothermic peak at 208.2°C, corresponding to the melting point of the drug.

The DSC thermogram of the DPC exhibits a sharp endothermic peak at 207.1°C. This could indicate no significant change in the crystallinity of AML due to formation of DPC with Eudragit EPO [14].

X-ray diffraction (XRD) studies: The XRD diffractograms of AML and (1:1 ratio) AML: Eudragit EPO DPC is depicted in **Fig. 2E & F**. The diffractogram of pure AML, confirms the crystalline nature of the drug, as demonstrated by numerous distinct peaks at 2θ of 16.31°, 18.79°, and 19.96°, 22.90° respectively (A); (i.e. Fingerprint region).

However, the intensity of the peaks in DPC (Fig.2B) was almost similar when compared to that of the pure drug. The results indicate that the drug in DPC had no significant change in the crystallinity as compared to the pure drug; hence the dissolution of the drug was not significantly changed [14].

Drug-excipient compatibility (FT-IR) studies: The FT-IR spectrum of AML (**Fig. 3A**) is characterized by sharp characteristic peaks at 3300.20, 3158.50, 1651.08, and 1616.08 cm^{-1}. All the above characteristic peaks appear in the (1:1 ratio) physical mixtures of AML with superdisintegrants (**Fig. 3B-E**) at same wavenumber indicating no modification or interaction in the drug with the combination of superdisintegrants used in the study [14].

Pre-compression studies: The directly compressible blends of AML SLT, reveals that the angle of repose was found between 17˚.2'to 22˚.4', Hausner's Ratio between 1.11 to 1.21 and Carr's index between 13.9 to 17.6 %. The micromeritic studies indicate good flow and compression characteristics of all the formulations.

In these formulations sugar based excipient, directly compressible mannitol is used as diluent, which imparts good flow and compressibility to the blends. It also exhibits good aqueous solubility along with sweetness and negative heat of solution, hence, it imparts a pleasant mouth feel [15] (**Table 2**).

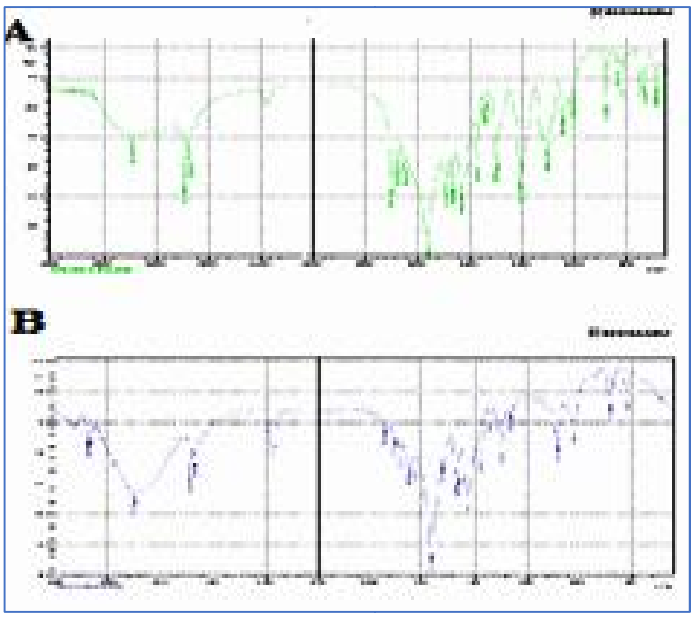

Fig 2: FT-IR spectra of A) AML, B) DPC;

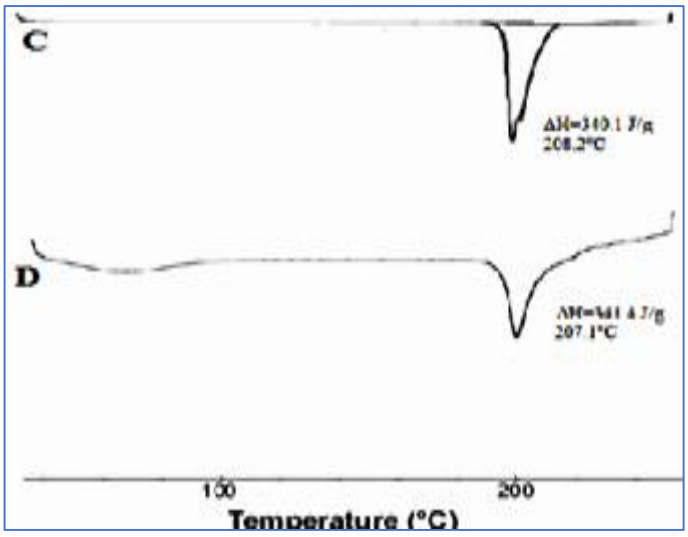

Fig 2: DSC thermograms of C) AML, D) DPC and;

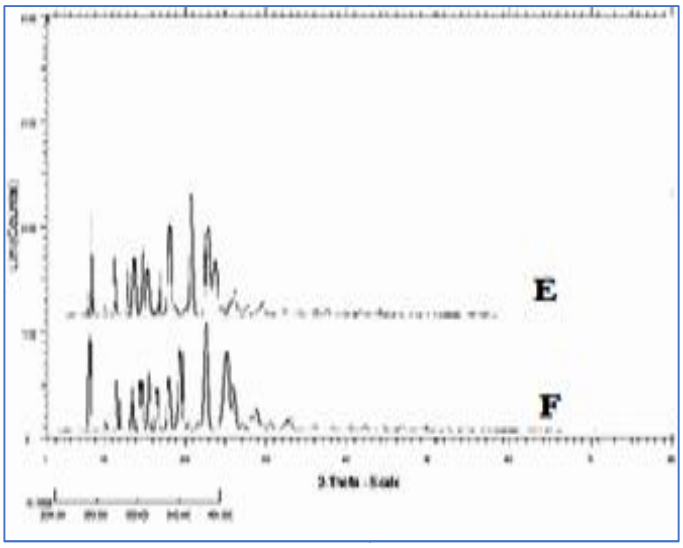

Fig 2: XRD diffractograms of E) AML, F) DPC

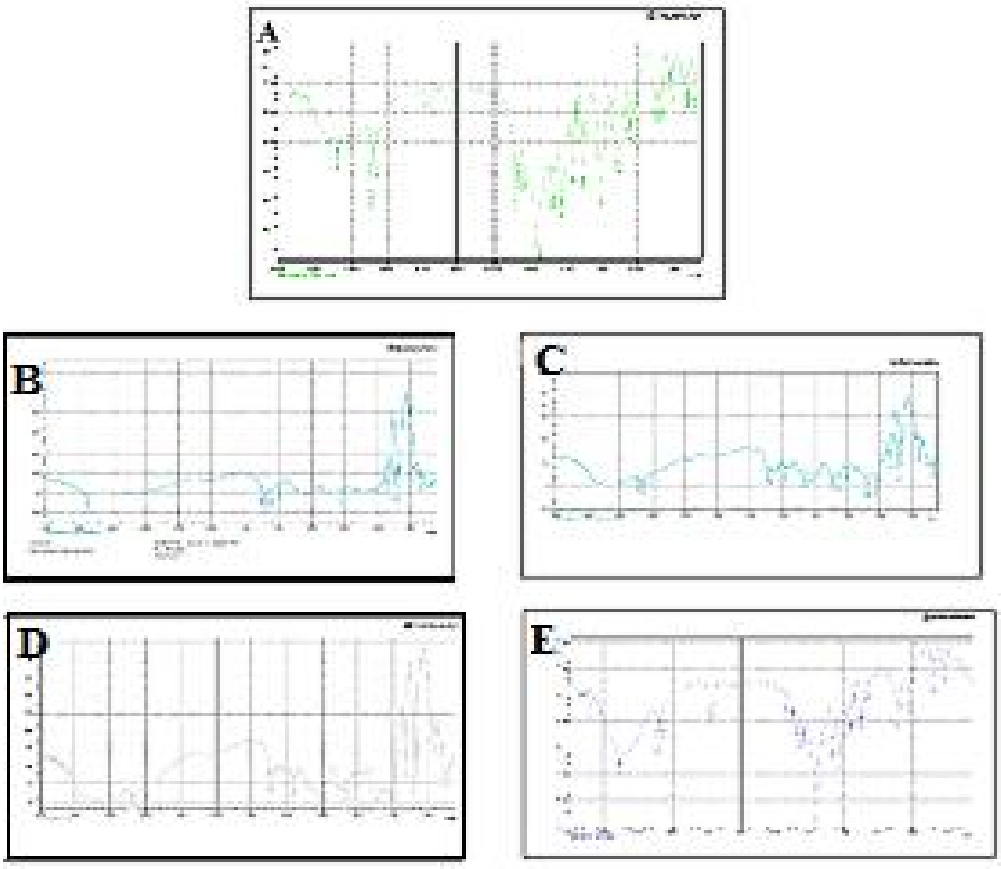

Fig. 3: FT-IR spectra of A) AML, B) AML + CPV, C) AML + CCS, D) AML + SSG, E) AML + SCMC

Table 2: Results of pre-compression studies of AML SLT.

F. Code	AR (θ)	BD (g/cm^3)	TD (g/cm^3)	CI (%)	HR
F1	22.4±0.02	0.49±0.02	0.57±0.22	16.1±0.12	1.12±0.12
F2	21.2±0.13	0.51±0.12	0.56±0.13	15.9±0.13	1.11±0.13
F3	19.7±0.07	0.51±0.15	0.57±0.21	17.6±0.18	1.19±0.18
F4	18.8±0.11	0.54±0.11	0.60±0.32	13.9±0.22	1.15±0.22
F5	17.2±0.15	0.52±0.32	0.56±0.07	14.8±0.20	1.18±0.20
F6	19.2±0.06	0.53±0.21	0.58±0.03	15.4±0.12	1.21±0.12
F7	19.8±0.12	0.51±0.13	0.55±0.14	14.4±0.14	1.16±0.14
F8	17.6±0.04	0.50±0.21	0.54±0.12	16.4±0.17	1.19±0.17
F9	17.2±0.06	0.49±0.23	0.50±0.11	17.9±0.17	1.21±0.17
F10	19.7±0.04	0.49±0.14	0.58±0.32	15.5±0.23	1.18±0.23
F11	20.2±0.01	0.50±0.24	0.59±0.25	15.3±0.25	1.18±0.25
F12	20.6±0.13	0.47±0.11	0.56±0.14	16.1±0.13	1.19±0.13

Post-compression studies: Of all the AML SLT, reveals that the Avg. Wt. of tablets of was found to be 148.3 to 150.8 mg. The Avg. thickness of tablets was found to be 2.3 to 2.7 mm. The Avg. hardness of the tablets ranges between 3.14 to 3.45 Kg/cm^2, indicating satisfactory mechanical strength. The % Wt. loss in the friability test ranges from 0.28 to 0.48 %, which was NMT 1 % as per pharmacopeia limits indicating a good mechanical resistance of tablets. Assay of all the prepared batches is within 96.92 to 98.72 % of the labelled content, indicating the content uniformity of all the formulations.

The disintegration test results show CPV achieved the fastest disintegration (< 25 sec), as it produces the highest tablet breaking force at a given compression force and croscarmellose sodium provided the slow disintegration (near to 1 min). The wetting time of all the formulations was obtained in the range of 21.12 to 70.11 sec. As the conc. of superdisintegrant increases, there is a significant decrease in the *in vitro* wetting and disintegration time. Wetting is related to the inner structure of the tablets, hydrophilicity of the components and swelling mechanism of superdisintegrant.

The swelling index is also related to the hydrophilicity of the matrix. The SLT with CPV were fully hydrated and soft throughout because CPV quickly wicks water into the tablet by imparting porosity [16].

Water wicking is the ability to draw water into the tablet matrix. Both the extent of water uptake and the rate of water uptake are critically important. Exposure to water can cause ingredients to swell and exert pressure against surrounding tablet or capsule ingredients, causing existing bonds between particles to break [17]. Water wicking and swelling are the two most important mechanisms of disintegrant action for CCS and SCMC [18]. SSG is a commonly used super disintegrant employed to promote rapid disintegration by swelling mechanism [19].

Although the tablets with SSG, SCMC and CCS are swollen, the centers of the tablets remained dry and hard and the outer edges appeared with gel like consistency. Studies have suggested that the water insoluble superdisintegrants show better disintegration property than the slightly water-soluble agents, since they do not tend to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier [20]. Hence, among the used superdisintegrants CPV is superior. The order of superdisintegrants efficiency was observed as CPV > SCMC >CCS > SSG. The formulation F3 (with 8 %w/w of CPV) which shows min wetting time of 21.12 sec and disintegration time of 17 sec, is considered as an optimal AML SLT (**Table 3**).

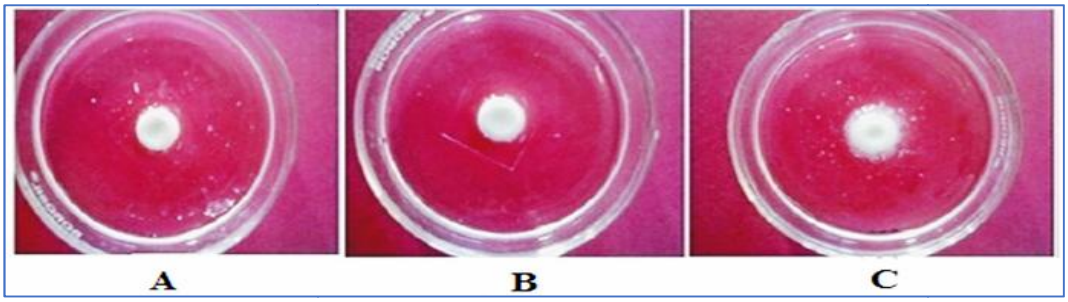

Fig. 4: Pictures while measuring wetting time of AML SLT; F3 A) Initial stage, B) at 10 sec and C) at 21.12 sec

Table 3: Results of post-compression studies of AML SLT

F. Code	Avg. wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)	DT (sec)	WT (sec)	SI (%)
F1	150.2±0.02	2.4±0.13	3.16±0.12	0.39	98.23±0.22	24±0.12	29.21±0.02	60.81±0.13
F2	149.4±0.12	2.3±0.02	3.14±0.13	0.37	97.89±0.13	20±0.15	26.14±0.07	65.09±0.21
F3	148.3±0.15	2.5±0.07	3.14±0.18	0.33	98.72±0.21	17±0.11	21.12±0.11	68.90±0.22
F4	150.2±0.32	2.4±0.11	3.15±0.22	0.41	98.34±0.32	35±0.32	38.26±0.15	56.04±0.20
F5	149.5±0.21	2.6±0.15	3.16±0.20	0.28	98.45±0.07	27±0.11	35.18±0.13	59.62±0.13
F6	150.4±0.13	2.3±0.06	3.19±0.12	0.48	99.24±0.03	25±0.02	31.12±0.06	61.90±0.12
F7	149.3±0.21	2.7±0.12	3.45±0.14	0.36	96.92±0.14	51±0.21	77.98±0.04	38.16±0.03
F8	148.2±0.23	2.5±0.04	3.30±0.17	0.39	98.15±0.12	49±0.14	75.34±0.01	44.17±0.17
F9	150.5±0.14	2.7±0.06	3.31±0.23	0.39	98.82±0.11	48±0.24	70.11±0.12	49.42±0.25
F10	151.1±0.24	2.5±0.04	3.23±0.17	0.48	97.98±0.32	32±0.13	58.23±0.04	49.14±0.14
F11	148.4±0.11	2.7±0.01	3.26±0.25	0.45	98.25±0.25	29±0.21	55.11±0.06	55.16±0.17
F12	150.8±0.15	2.6±0.13	3.21±0.13	0.37	98.63±0.14	25±0.23	53.72±0.13	59.46±0.23

* Except for Avg. wt. and friability test all other were performed in triplicate (n = 3) and the values are expressed as (mean ± SD).

***In vitro* dissolution studies:** *In vitro* dissolution profiles of pure AML and (1:1) ratio of AML: Eudragit EPO DPC is represented graphically (**Fig. 5**) indicate that there is no significant difference in the dissolution rate of AML due to the formation of complexes with Eudragit EPO. *In vitro* dissolution profiles of AML SLT are represented graphically in **Fig. 6** indicate that, the release rate increases with an increase in concentration of superdisintegrant. Based on the values of first order dissolution rate constant (K_1); the order of superdisintegrants in enhancing the dissolution rate of AML from its fast disintegrating SLT is CPV > SCMC >CCS > SSG. Formulation F3 (with 8% CPV) released 98.75 % of the drug within 20 min compared to others, is considered as an optimal AML SLT (Fig. 6).

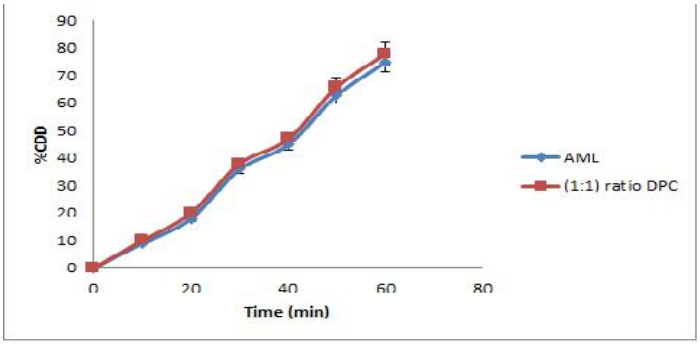

Fig. 5: *In vitro* dissolution profiles of A) pure AML & B) (1:1) ratio of AML: Eudragit EPO DPC.

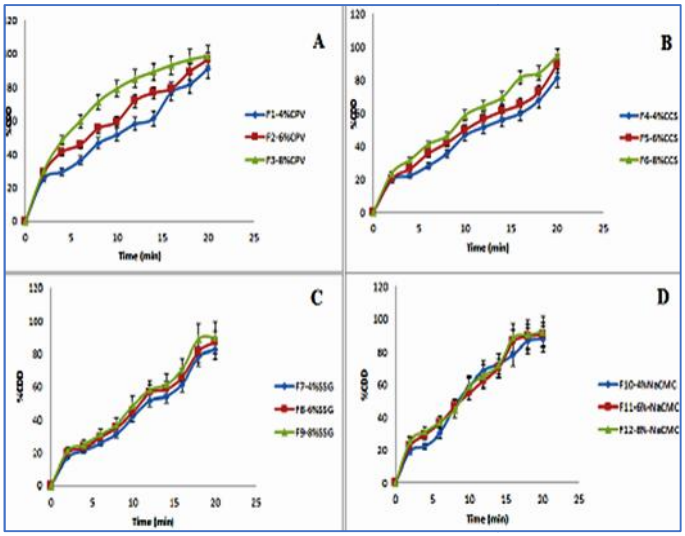

Fig. 6: *In vitro* dissolution profiles of A) AML SLT with CPV B) AML SLT with CCS C) AML SLT with SSG & D) AML SLT with SCMC

In vitro dissolution kinetics: Reveals formulation F3 had the highest DE_{10} (49.80 %); K_1 (0.198min^{-1}) with r^2 (0.956) and lowest t_{50} (< 6 min). Hence, it is an optimal AML SLT (**Table 4**).

Table 4: *In vitro* dissolution kinetics of AML SLT

F. Code	Dissolution plots		First order plots	
	t_{50} (min)	DE_{10} (%)	K_1 (min^{-1})	r^2
F1	< 10	32.78	0.102	0.894
F2	< 8	40.14	0.133	0.877
F3	< 6	49.80	0.198	0.956
F4	< 12	25.76	0.070	0.922
F5	< 12	29.81	0.087	0.856
F6	< 10	34.40	0.120	0.893
F7	< 12	23.33	0.079	0.905
F8	< 12	25.87	0.090	0.896
F9	< 12	27.80	0.108	0.864
F10	< 10	29.78	0.109	0.976
F11	< 10	32.65	0.122	0.931
F12	< 10	33.70	0.131	0.926

Accelerated stability studies of the optimized AML SLT; F3: There were no significant differences in post compression studies of initial and accelerated stability samples of optimized formulation F3 up to 3 months in a 20 cc HDPE pack, hence it passes the test for stability as per ICH guidelines. (**Table 5 & Fig. 7**)

Table 5: Results of post-compression studies on accelerated stability samples of opt. AML SLT; F3.

Parameter	Initial	45°C / 75%RH		
		1M	2M	3M
Avg. wt. (mg)	148.3±0.15	150.2±0.21	150.5±0.11	150.8±0.22
Thickness (mm)	2.5±0.07	2.6±0.12	2.6±0.15	2.7±0.01
Hardness (kg/cm^2)	3.14±0.18	3.14±0.21	3.12±0.12	3.11±0.25
***Friability (%)**	0.33	0.36	0.38	0.41
Assay (%)	98.72±0.21	99.35±0.12	99.25±0.13	99.21±0.09
DT (Sec)	17±0.11	17±0.11	16±0.11	15±0.11
WT (Sec)	21.12±0.11	20.122±0.24	19.35±0.31	18.22±0.23
SI (%)	68.9±0.22	70.34±0.14	73.45±0.07	76.31±0.13

* Except for Avg. wt. and friability test all other were performed in triplicate (n = 3) and the values are expressed as (mean ± SD).

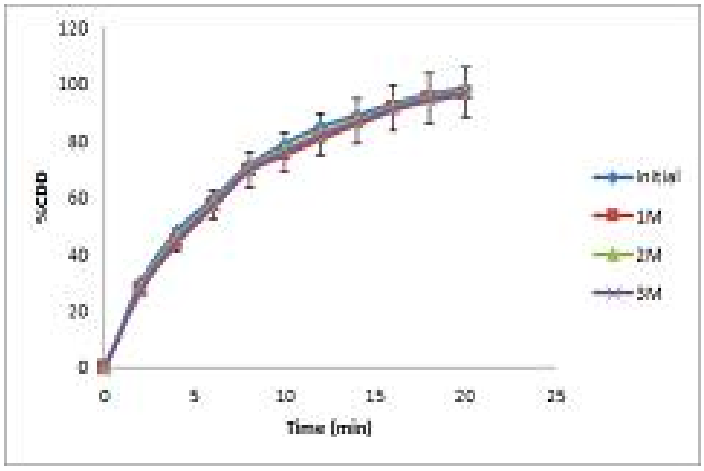

Fig. 7: Dissolution profiles of accelerated stability samples of optimized AML SLT; F3.

CONCLUSION

In the view of the above findings, there is drug-excipient compatibility between AML, Eudragit EPO and super-disintegrants used in the study. Results of physicochemical characterization of DPC indicate there is no modification or interaction in the drug in DPC by FT-IR studies and no significant change in the crystallinity of AML due to formation of DPC by DSC and XRD studies. All the formulations passed the pre- & post- compression evaluation parameters. *In vitro* dissolution profiles of pure AML and (1:1) ratio of AML: Eudragit EPO DPC indicates there is no significant difference in the dissolution rate of AML due to the formation of complexes with Eudragit EPO. The drug release rate of AML from its SLT increases as the concentration of superdisintegrants increases. The order of superdisintegrants in enhancing the dissolution rate of AML is CPV > SCMC >CCS > SSG.

Formulation F3 (with 8 % CPV) which shows min wetting time of 21.12 Sec and min disintegration time of 17 Sec, had the highest DE_{10} (49.80 %); K_1 (0.198 min^{-1}) with r^2 (0.956) & lowest t_{50} (< 6 min), was considered as the optimal SLT. Accelerated stability studies on optimized AML SLT; F3 in the final 10 cc HDPE pack up to 3 months, indicate it passes the test for stability as per ICH guidelines. Therefore, an effective fast dissolving AML SLT for treating hypertension and angina was formulated by the direct compression technique, with taste masked by Eudragit EPO at equal concentration of the drug, by hot melt extrusion technique and combination of artificial flavor and sweeteners. The fast dissolution rate was attained by 8 % w/w CPV as superdisintegrant. This novel formulation will fasten the onset of action and thereby enhances the bioavailability of AML in comparison to its conventional tablets, with enhanced patient compliance due to effective taste masking.

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REFERENCES

1. Sharma S and G D Gupta. Formulation and characterization of fast dissolving tablet of Promethazine Theoclate. *Asian J. Pharm.* 2008; 2(1): 70-72.
2. Nehal Siddiqui M, G Garima and P K Sharma. Fast dissolving tablets: preparation, characterization and evaluation. *International Journal of Pharmaceutical Sciences Review and Research.* 2010; 4(2): 87-96.
3. Berner B, Birudaraj R, Shen S, Li X. Buccal permeation of buspirone: mechanistic studies on transport pathways. *J Pharm Sci*. 2005; 94: 70- 78.
4. Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH- M- 06) and spherical sugar granules. *Chem Pharm Bull (Tokyo).* 2001; 49: 230- 32.
5. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single- dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta- estradiol. *Obstet Gynecol.* 1997; 89: 340- 45.
6. Ohmori M, Arakawa M, Takasali H, Hifumi S, Fujimura A. Stereoselective pharmacokinetics of amlodipine besylate in elderly hypertensive. *Am J Ther*. 2003; 10: 29- 31.
7. Rajendra Messa, Srinivas Ampati. Formulation and evaluation of Mouth Dissolving Tablets of Amlodipine Bisylate. *International Journal of Medicine and Nanotechnology.* 2015; 2(5): 289-94.
8. B. Sree Giri Prasad, V.R.M. Gupta, N. Devanna, N. Siva Subramanian, Ch. Naveen Kumar, Ch. Maheswar Reddy. Formulation and evaluation of taste masked Orodispersible tablets of Amlodipine Besylate by direct compression. *International research journal of pharmacy.* 2013; 4(7): 123-30.
9. Banker GS, Anderson NR, Lachman L, Liberman HA. The Theory and Practice of Industrial Pharmacy, 3rd ed. Mumbai: Varghese Publishing House; 1987, p: 293-94.
10. European Pharmacopeia 6th ed. Strasburg, France; 2007, p: 2435.
11. Gautam Singhvi, Mahaveer Singh. Review: *In vitro* Drug Release Characterization Models. *International Journal of Pharmaceutical Studies and Research.* 2011; 2(1): 77-84.
12. D.M. Brahmankar; Sunil. B. Jaiswal. Bio-pharmaceutics and Pharmacokinetics: A Treatise. 2nd ed. New Delhi: Vallabh Prakashan; 2009, p: 254-55.
13. http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisation/SADC/Guideline_for_Stability_Studies.pdf
14. Jatinder Kaur, Geeta Aggarwal, Gurpreet Singh, A.C. Rana. Formulation and evaluation of Fast Dissolving Tablet Containing Amlodipine Besylate Solid Dispersion. *Int J Pharm Pharm Sci.* 2012; 4(1): 409-16.
15. Duriez X, Joshi AA. Starches: A Versatile Source. *Pharma Form. Qual*. 2004; 6 (3): 48-50.
16. Rakesh Pahwa and Nisha Gupta. Superdisintegrants in the Development of Orally Disintegrating Tablets: A Review. *International Journal of Pharmaceutical Sciences and Research.* 2011; 2(11): 2767-80.
17. Parakh SR, Gothosakar AV. A Review of Mouth Dissolving Tablet Technologies. *Pharm Technol.* 2003; 27 (11): 92-100.
18. Weller PJ. Croscarmellose Sodium. Ainely Wade and Paul (London). 1994; 2: 141- 42.
19. Banker GS. Sodium Starch Glycolate. 2nd ed. Ainely Wade and Paul, London. 1994.
20. Duriez X, Joshi AA. Starches A Versatile Source. *Pharma Form. Qual.* 2004; 6(3): 48–50.

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