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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF LOPERAMIDE

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ABSTRACT: Purpose of present research work was to develop mouth dissolving tablets of loperamide using superdisintegrants. Mouth dissolving tablets of loperamide were prepared by direct-compression method after incorporating superdisintegrants Ac-Di-Sol, Sodium Starch Glycolate (SSG), and Crosspovidone in different concentrations. Effect of superdisintegrants on disintegration and dissolution behavior of tablet in 0.1 N HCl, phosphate buffer (pH 6.8) was evaluated. To address poor solubility of loperamide, solid dispersion using solvent evaporation techniques was prepared using hydrophilic carrier PEG4000, PVP K-30, and Urea. Improvement in dissolution of drug was observed in solid dispersion as compared to pure drug. The 100% drug release was obtained from the solid dispersion (prepared by solvent evaporation method) of Loperamide: PEG4000 (1:6) in 10 minute. Formulations were evaluated for Weight variation, hardness, and thickness, friability, wetting time uniformity of dispersion, drug content, disintegration time and in vitro dissolution studies. The drug content of all the formulations was within the acceptable limits of the United States Pharmacopoeia XXVII. Optimized formulation showed good release profile with maximum drug being released at all-time intervals. Optimized Formulation (F-8) containing crosspovidone showed > 90% drug release in 20 min and disintegration time of 17 sec. From Stability point of view no appreciable change was observed in release profile and drug content after 3 month storage of tablet at 40±2° and 75±5% RH.

INTRODUCTION: Loperamide 4-[4-(4-chloro phenyl)-4-hydroxypiperidin-1-yl]-N, N-dimethyl-2, 2-diphenylbutanamide is a poorly water soluble drug used in the treatment of diarrhoea (solubility <1 mg/100 ml). It is commercially available as a hydrochloride salt under the trade name Imodium in order to overcome the problem of poor solubility and hence poor oral bioavailability¹.

The aim of this study was to use loperamide as a model compound to explore another route to tackle this problem, i.e. the use of solid dispersions. They are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state, prepared by the fusion, solvent or solvent-fusion method. These systems provide the possibility of;

- (a) reducing the particle size of the drugs to (nearly) a molecular level,
- (b) locally increasing the saturation solubility and/or;
- (c) of transforming the drug from the crystalline to the (partially) amorphous state.

Mouth dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of Mouth dissolving tablets, which in turn prolongs the patent life of a drug. Keeping in view of the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular^{2,3}.

MATERIAL AND METHODS: Loperamide was procured from Well cure pharma Indore (M.P.) India. Urea, PEG-4000 and PVP K-30 were of pharmaceutical grade and obtained commercially. Ac-di-sol, Crospovidone, Avicel pH 102 was procured from Lupin Research Center pune (M.H.) India. Aspartame, Mannitol SD-200 DC (perlitol) procured from Plethico pharmaceuticals Ltd. Indore (M.P.). Talc, Magnesium Stearate was purchased from Loba Chemie Pvt. Ltd. Mumbai. All solvent used were of analytical grade and were purchased from Merck Ltd. Mumbai (M.H.) India.

Preparation of Solid Dispersion:

1. **Solvent evaporation method:** Loperamide, PEG-4000 PVP-K-30 and Urea were weighed accurately in the ratio of 1:1, 1:3 and 1:5 and triturated in a mortar pestle for 5 minutes and dissolved in 50 ml of methanol with constant stirring. The solvent was evaporated at 45°C and dried in a desiccator for 12 hrs and passed through sieve No. 60⁴.
2. **Preparation of Physical mixtures:** Loperamide was taken with PEG 4000, PVP K-30 and Urea, in the ratio of 1:1, 1:3 and 1:5 and triturated in a mortar and pestle for 15 minutes and kept in a dessicator for further use⁵.

3. **Solubility study of various type of solid dispersion:** The solubility studies were performed by taking 10 mg drug equivalent of solid dispersion from the each batch (SD-A, SD-B and SD-C) were dissolved in water and PBS (pH6.8) and kept in mechanical shaker for 30 min at 30°C. Sample was taken after 30 min from each volumetric flask and was analyzed spectrophotometrically at 259 nm⁶.

The solubility studies were performed by taking 10 mg drug equivalent of physical mixture from the each batches (PM-A, PM-B and PM-C) and dissolved in water and PBS (pH6.8) kept in mechanical shaker for 30 min at 30°C. Samples were taken after 30 min from each volumetric flask and absorbance were measured by UV-visible spectrophotometer⁷.

Characterization of Solid Dispersion: The drug and the prepared solid dispersions were evaluated for drug content, thin layer chromatography, FTIR Spectroscopy, In-vitro dissolution studies.

Drug content: Accurately weighed quantity of solid dispersion, equivalent to 10 mg loperamide was dissolved in 10 ml of methanol by using mechanical shaker for 30 min. and filtered using whatman filter paper and absorbance was measured at 259 nm by UV-visible spectrophotometer⁸.

Thin Layer Chromatography: Solid dispersions were subjected to TLC using pure Loperamide as a reference sample. The solvent system for TLC of Loperamide was chloroform, methanol, and formic acid (25.5: 3: 1.5). The R_f value of pure drug Loperamide and its Solid dispersion wear calculated.

FTIR of Solid Dispersion: FTIR spectrum of solid dispersion was taken from solid powder material and compared with pure loperamide spectrum.

In-vitro dissolution studies: Dissolution studies were conducted using a type II (paddle) USP dissolution apparatus with 900 ml PBS 6.8 pH as dissolution media. The temperature of the medium was maintained at 37°C ± 0.5 and RPM set as 50. The drug was assayed spectrophotometrically at 259 nm⁶.

Formulations of mouth dissolve tablets for loperamide: Drug Polymer complex (solid dispersion) and all Excipients were passed through

sieve no 60. Drug polymer complex, directly compressible Mannitol, Superdisintegrants (Sodium starch glycolate, Croscarmellose Sodium or Crospovidone), Microcrystalline Cellulose PH 102,

Aspartame, Vanilla flavor, Talc were mixed together for 20 min. Magnesium stearate, was then added and mixed for 5 min. Then blend of drug and Excipients to compress on Single punch machine **Table 1**⁶.

TABLE 1: FORMULATION DESIGN OF MOUTH DISSOLVING TABLETS

FORMULATION INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersion (Equiblent 8 mg drug)	54.68	54.68	54.68	54.68	54.68	54.68	54.68	54.68	54.68
Mannitol SD-200 DC (perlitol)	214	214	214	214	214	214	214	214	214
Microcrystalline cellulose	102.32	101.32	100.32	102.32	101.32	100.32	102.32	101.32	100.32
Ac-Di-Sol (Crosscarmellose sodium)	10	11	12	-	-	-	-	-	-
Sodium starch glycolate (Explotab)	-	-	-	10	11	12	-	-	-
Polyplasdon XL (Crosspovidone)	-	-	-	-	--	-	10	11	12
Aspartame	15	15	15	15	15	15	15	15	15
Vennila Flavor	2	2	2	2	2	2	2	2	2
Megnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total	400								

Evaluation of Mouth Dissolving Tablets: The Formulated mouth dissolving tablet were evaluated for different parameters like General characteristic, uniformity of weight, hardness, wetting time, Uniformity of dispersion, Disintegration test, Drug release study **Table 2**⁸.

General characteristic: General appearance of tablet, its visual identity size, shape, color of the tablet was evaluated.

Uniformity of Weight: 20 tablets of each batch were collected randomly during compression and weight of individual tablets was carried out.

Hardness or Friability: For each formulation the hardness and friability of 6 tablets wear determined using Monsanto hardness tester and the Roche Friabilator.⁹

Content of Active Ingredients: The amount of active ingredient was determined by the method described in the drug content. By crushing the 10 tablets and taking powder equivalent to 8 mg Loperamide. Then this powder dissolved in 100ml 0.1N HCl appropriate dilution of the resulting solution was prepared and absorbances of the resulting solution were taken UV

Spectrophotometrically. % drug content has been calculated.

Wetting time: Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimeters of water-containing methyl red, a water-soluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time¹⁰.

Disintegration test: Apparatus for Disintegration of Tablets and Capsules according to Indian pharmacopoeia 1996 used for the determination of disintegration test for dispersible tablets. The beakers containing the 900ml distilled water at 25 ±1°C and operate the apparatus for three min. and remove the assembly from the liquid. The tablets pass the test if all of them have disintegrated. Dispersible tablets should disintegrate within 3 minutes when examined by the disintegration test according to Indian Pharmacopoeia 1996.

Uniformity of Dispersion: This test is applicable only to Dispersible Tablets. Place 2 tablets in 100 ml of water and stir gently until completely dispersed. A smooth dispersion is obtained which passes through

a sieve screen with a nominal mesh aperture of 710 μm (sieve number 22).

Drug release study in simulated salivary fluid pH 6.8 & 0.1 N HCl: The drug release method for mouth dissolving tablets is comparable to the approach to the approach taken for conventional tablets, and is practically identical. The release study carried out in USP Type 2 dissolution apparatus containing 900ml 6.8 pH phosphate buffer and 0.1 N HCl at 50 rpm and 37°C temperature. The drug release sample 5ml withdrawal by suitable time interval and fresh dissolution medium were added in the each withdrawal. Then appropriate dilution of the samples has been prepared and absorbances of the resulting solution were taken spectrophotometrically¹¹.

Stability study: Stability study was conducted by storing the tablets at 40±2°/75±5% Relative humidity for three months. The content, hardness, weight variation and release behavior from dissolving tablets were tested after three month (ICH guidelines).

RESULTS AND DISCUSSIONS: Prepare solid dispersion and physical mixture ratio 1:1, 1:3, 1:5 with PEG4000, PVP k-30 and urea optimize by best solid dispersion and physical mixture of solubility process with PBS and water. According to observations obtained the solubility of the SD-A (Drug-Peg4000) was found maximum it show that the drug was enhanced with increasing the quantity of peg4000 and observations obtained in the physical mixture no significant change seen in the solubility of drug as compared to pure drug in this study best result found in the drug-peg4000 complex solid dispersion this is select for final solid dispersion.

For further study performed final solid dispersion prepare different ratio of solid dispersion ratio 1:2,1:4,1:6,1:8 according to observations obtained various media solubility of SD-III show maximum. Prepared solid dispersions SD-2, SD-2, SD-3, and SD-4 evaluated for drug content 97.60%, 96.3, 98.90, 94.20 respectively. The TLC studies show clear resolution for solid dispersion system. RF value of loperamide, drug+peg4000 and drug+PVP K-30 is 1.43:1.38:1.46 respectively.

The FTIR data was compared with the standard spectrum of loperamide and the characteristics peaks associated with specific structural characteristics and

their presence in polymeric carrier as well as solid dispersion were noted.

The drug showed major peaks at 1447 cm^{-1} for C-O-H, 1375 cm^{-1} for $-\text{CH}_3$, 1036 for R-Cl and peak 1622 cm^{-1} for $-\text{C}=\text{O}$ appears aliphatic ketone and peak between 770-735 cm^{-1} for characteristic aromatic hydrocarbon. Solid dispersion exhibited peaks of the drug and the carriers. The IR spectra (Fig 1) of solid dispersion PEG4000 complex exhibited characteristic drug peak 1622 cm^{-1} and 1375 cm^{-1} broadening due to overlapping between solid dispersion of PEG 4000, $-\text{C}-\text{C}-$ of the drug perhaps result in increased solubility. This indicates that solid dispersion spectra were only the summation of loperamide and PEG4000 spectra and it reflects that there was no major interaction between loperamide and PEG4000.

Solid dispersion of drug and PVP K-30 complex shows that 1375 cm^{-1} characteristic drug peak ($-\text{CH}_3$) are negligible and broadening of peak summation of loperamide and PVP K-30 (1652-1622 cm^{-1}) shows interaction between drug and PVP K-30 complex. There was major interaction between loperamide and PVP K-30.

In IR spectrum drug-Urea complex solid dispersion, broadening of aliphatic ketones peak 1622 cm^{-1} is due to $-\text{NH}$ group of urea that interacts with $-\text{CH}_3$ group of loperamide. This indicates major interaction between loperamide and Urea. The FTIR spectra of solid dispersion drug- PEG-4000 (Fig 1) showed that there was no significant interaction between drug and carrier.

In-vitro dissolution studies pure loperamide and different ratio of final solid dispersion according to drug contents (10mg drug containing) using type-II (paddle) USP dissolution apparatus with 900 ml PBS pH 6.8 at 37 ± 0.5 and rpm 50. the initial % drug dissolved in 1 hour loperamide slowest dissolution only 29.49% and SD-1, SD-2, SD-3 and SD-4 dissolve 99% in 45, 30, 25 and 25 respectively. Comparative % drug dissolution from solid dispersions in 25 min. 79.45%, 97.99%, 99.10% and 99.02% respectively.

Mouth dissolving tablets of Loperamide were prepared by superdisintegrants addition method and evaluated for various evaluation parameters of the tablets. Total nine formulations were designed (table 1). The hardness of tablets from all formulations was

in between 1.76 to 3.56 kg/cm². All the formulations showed friability below 0.91%. All the tablets were found to pass the uniformity of weight (table 2). Content of Loperamide from all formulation was found in range of 94.09% to 97.15% (table 2).

All the formulations tablets disintegrate in 15 to 22 S respectively (table 2). The wetting time was measured and found in range of 41.66 to 71.00 S (table 2).

TABLE 2: EVALUATION OF MOUTH DISSOLVING TABLETS

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
General characteristic	Complies								
Uniformity of weight	pass								
Hardness(kg/cm ²) ±S.D	3.23±0.20	2.66±0.23	2.90±0.29	1.83±0.23	1.76±0.20	3±0.40	2.83±0.23	3.56±0.49	3.33±2.23
Friability (%) ±S.D	0.75±0.02	0.68±0.01	0.75±0.03	1.46±0.18	1.23±0.20	0.91±0.02	1.5±0.24	0.74±0.02	0.69±0.02
Uniformity of content (%)±S.D	96.22±1.27	94.09±0.53	97.15±1.47	94.98±0.79	95.10±0.45	95.65±0.66	96.83±0.37	94.41±0.96	94.47±2.03
Wetting time (sec.) ±S.D	49±8.03	44.66±1.69	41.66±2.49	48±2.44	59.33±2.49	53.33±2.49	48.33±2.86	71±2.16	44.66±10.84
Uniformity of dispersion	pass								
Disintegration time (%)±S.D	23±0.123	11±0.156	8±0.156	13±0.365	26±0.659	15±0.135	17±0.326	20±0.156	19±0.732

*All the values expressed in mean± standard deviation (n=3)

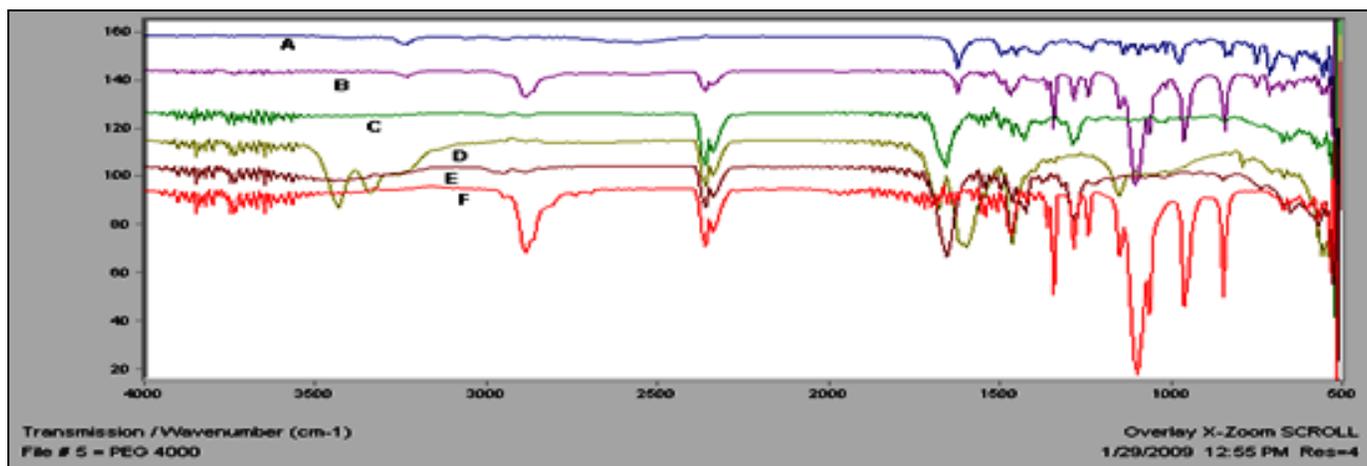


FIG. 1: FTIR SPECTRA OF (A) LOPERAMIDE (B) LOPERAMIDE PEG4000 COMPLEX (C) LOPERAMIDE PVP K-30 COMPLEX (D) LOPERAMIDE UREA COMPLEX (E) POLYVINYL PYRROLIDINE (PVP K-30) (F) POLYETHYLENE GLYCOL (PEG 4000)

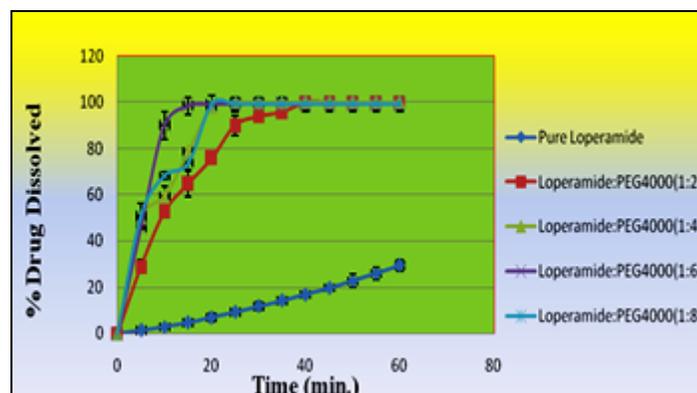


FIG. 2: COMPARATIVE % DRUG DISSOLUTION FROM PURE LOPERAMIDE AND SOLID DISPERSIONS

Superdisintegrants Polyplasdone XL (Crospovidone) batch no. LT –VIII displays best results among nine batch of the Mouth dissolving tablet. The *in-vitro* release study was carried out using 900 ml of 6.8 pH phosphate buffer and 0.1N HCl as dissolution medium at 50 rpm using USP dissolution apparatus. Formulation LT-VIII showed rapid dissolution and cumulative drug release at the end of 40 min. was more than 98% in 6.8pH phosphate buffer and in case of 0.1N Hcl, 99% drug release in 20 min (Fig. 3 & Fig. 4).

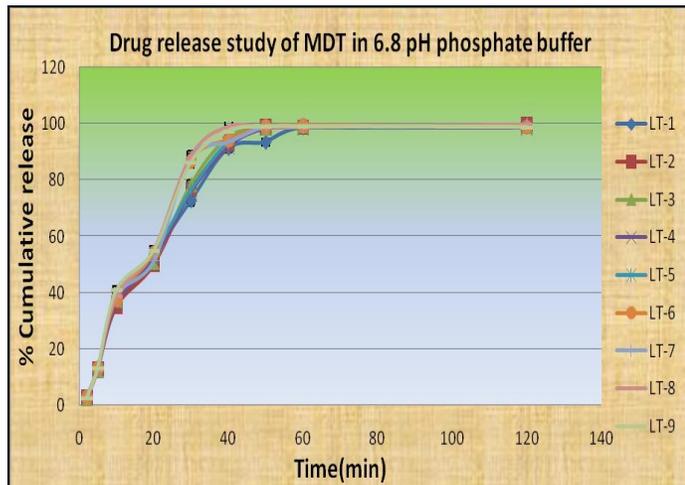


FIG. 3: DRUG RELEASE STUDY OF MDT IN SIMULATED SALIVARY FLUID PHOSPHATE BUFFER 6.8pH

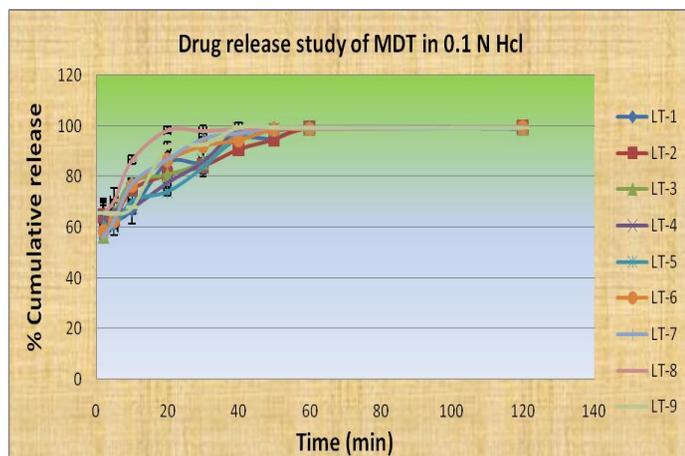


FIG. 4: DRUG RELEASE STUDY OF THE MDT IN SIMULATED GASTRIC FLUID pH 1.2

In-vitro release profile of conventional marketed tablet and pure drug superdisintegrants formulation and optimized LT-VIII were performed. Solid dispersion formulation (Fig. 5).

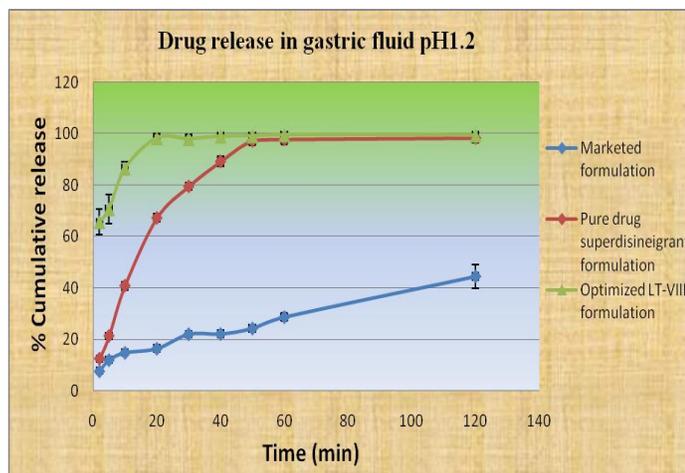


FIG 5: DRUG RELEASE STUDY OF MARKETED, PURE DRUG SUPERDISINTEGRANTS AND OPTIMIZED SD FORMULATION (LT-VIII) IN GASTRIC FLUID pH 1.2

LT-VIII gave far better dissolution than the conventional marketed tablet. Conventional marketed tablet releases only 16.52% drug while pure drug superdisintegrants tablets releases 67.22% drug in 20 min and LT-VIII exhibited almost 99.02% drug release in 20 min. The present dissolution efficiencies of conventional market tablet, pure drug superdisintegrants tablet and LT-VIII.

Tablets at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for Three month, were tested for their contents, hardness, weight variation and release behavior. It was observed that content from the tablets shows no appreciable change (Fig. 6).

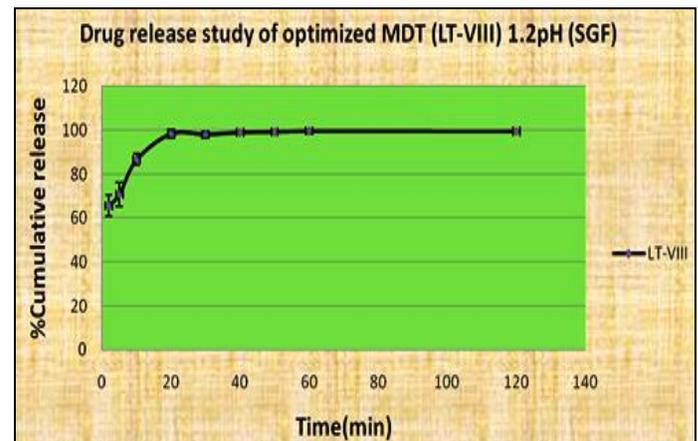


FIG 6: %CUMULATIVE DRUG RELEASE STUDY OF OPTIMIZED MOUTH DISSOLVING TABLETS OF LOPERAMIDE (LT-VIII) AFTER THREE MONTH STABILITY STUDY PERIOD

CONCLUSION: It can be concluded that the improvement in the dissolution of the poorly water soluble drug Loperamide through solid dispersion of solvent evaporation, which was obtained stable powder that possessed superior bioavailability and suitable for geriatric population and erratic absorption profile. Solid dispersion system of Loperamide can be used to enhance the *in-vitro* dissolution rate and bioavailability, due to improvement in wettability and solubilisation effect by the hydrophilic carrier (PEG4000, PVP-K-30 and Urea) at dissolution site.

Overall, the results suggest that suitably formulated mouth-dissolving tablets of Loperamide containing super disintegrants (croscarmellose sodium, sodium starch glycolate, crospovidone). The tablets exhibited good *in-vitro* disintegration and wetting properties in presence of Super-disintegrants.

The present study demonstrate that mouth dissolving tablet using solid dispersion have enormous potentials for increasing dissolution and finally the bioavailability of the drug.

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