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FORMULATION DEVELOPMENT AND EVALUATION OF LISINOPRIL FAST DISSOLVING TABLET.

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This research work aimed to develop and analyze fast dissolving tablets (FDT) of Lisinopril, which is an antihypertensive agent, using different superdisintegrants, Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), and Crospovidone (CP). The direct compression method was used to prepare the tablets and the formulations were optimized on the basis of in-vitro drug release properties of the tablets, which were similar to the marketed product. Formulation F8, which incorporates 10% w/w Crospovidone was taken as the optimized formula because of its fast rate of dissolution, as it releases 99.88% of the drug within 10 minutes. The formulation was found to be stable when stored at various conditions such as 25 C +/- 2 C and 60% +/- 5 RH and 40 C +/- 2 C and 75% +/- 5 RH over a period of 12 weeks. Stability studies exhibited little changes in physical parameters and drug release, which demonstrated that the optimized formulation is stable under accelerated conditions. Kinetic investigations indicated that the drug release was of first-order kinetics and the mechanism of drug release was dominated by diffusion. The Fourier Transform Infrared (FTIR) spectroscopy showed that the drug experienced weak intermolecular interactions with the excipients. The formulated FDT has a potential benefit in fast drug absorption, giving an immediate relief to hypertensive patients. It is suggested that further research involving bioequivalence analyses and market appropriateness assessments be performed.

Key words: Tablet, Fast Dissolving, Compression, Lisinopril.

INTRODUCTION

Tablets can be prepared using one of two methods: compression or moulding. Excipients are substances that ensure that tableting is carried out efficiently, including diluents, binders, glideants, lubricants; disintegrants to dissolve the tablets in the digestive system; sweeteners or flavors to enhance the visual appearance of tablets or assist in identifying unknown tablets visually (Mestel, Rosie *et al.*, 2015 & E. Plaza *et al.*, 1994). It is common practice to coat tablets with polymers in order to make them swallowable, control the release rate of active

used to be determined by the color of the components that make up the tablet, but now they are made in a variety of shapes and colours, so that they can be distinguished from one another in order to protect the patient's health. It is also common to find tablets imprinted with symbols, letters, and numbers, in addition to symbols, letters, and numbers, or grooves, for the purpose of splitting them by hand. A swallowable tablet usually varies in size from a few millimeters to around a centimeter in length, depending on its shape and size.

Initially, tablets took the form of disks of color determined by their components, but today's tablets can be made in a variety of colors and shapes to assist with their differentiation. Tablets are often imprinted with symbols, letters, and numbers to make them easy to identify, or grooved so that they may be manually split. Various sizes of tablets can be swallowed, ranging from a

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ingredients, extend the shelf life of tablets, and improve their appearance as well The shape of medicine tablets

few millimeters to about one centimeter (A Gupta *et al.*, 2010).

Fast Dissolving Tablets

A rapid increase in demand has resulted in a highly competitive market for drug delivery technology. Among the many new and innovative delivery systems emerging from the field of rapid dissolving technology, rapid dissolving tablets (FDTs) are gaining popularity. Oral administration is the most convenient and safest method of administering a wide range of drugs. It has recently been discovered that fast-dissolving tablets can be dissolved in saliva without the use of water. It is effectively used in situations where there is no access to water to use FDTs and MDTs (mouth-dispersing tablets). It is also possible to use FDT as an alternative to traditional dosage forms. The various ways in which FDTs can be prepared, the patents available, the mechanisms of superdisintegration, challenges encountered, and limitations associated with FDTs (Chhote Lal Singh *et al.*, 2014).

MATERIALS AND METHODOLOGY

The study materials are Lisinopril, Sodium starch glycolate, Croscarmellose sodium, Crospovidone, Microcrystalline cellulose, Mannitol, Aerosil, Sodium saccharin, Magnesium stearate, Potassium dihydrogen phosphate, Sodium hydroxide and Talc. UV-Spectroscopy method was used to develop the standard curve of Lisinopril. In the preparation of Sorenson's buffer at pH 6.8, a 0.2 M Potassium dihydrogen phosphate solution (primary solution) was prepared by dissolving 27.218 grams of the salt in a little distilled water and bringing the volume to one litre. In a separate case, 0.2 M Sodium hydroxide solution (secondary solution) was obtained by dissolving 8 grams sodium hydroxide in distilled water as well as adjusting the volume to one litre. In order to prepare Sorenson buffer, 50 ml of primary solution and 22.4 ml of the secondary solution were combined and the volume was made up to 200 ml with distilled water and the final pH was determined and adjusted to 6.8

Preformulation Studies

One important factor of the preformulation studies is drug-excipient compatibility, to guarantee the final pharmaceutical formulation stability and efficacy. To be able to judge the flow properties of powder blends is crucial to the uniformity of the formulation and can commonly be determined by the angle of repose, being the maximum angle between the surface of a pile of powder and the horizontal plane, by allowing the powder to flow through a funnel to form a cone. Also, loss on drying (LOD) determines the moisture and volatile matter in a sample by weighing the sample before and after drying at a given condition. bulk density (ρ_b) is

the mass of the powder divided by the bulk volume, and tapped density (ρ_t) is the density measured after mechanically tapping the container until the volume stops changing. Flowability is also determined by Hausner ratio (HR) and Carr's Index (CI) where Hausner ratio is the ratio between tapped density and bulk density of the powder and Carr's Index is the percentage compressibility of the powder-both are measures of powder flow propensity (Milinković S *et al.* 2024)

The fast-dissolving tablets (FDT) of Lisinopril were prepared by direct compression method with three different concentration (5%, 10%, and 15%) of each superdisintegrant. The exact formulas of the FDT formulations are given in the respective table. Lisinopril, superdisintegrants, mannitol-D, microcrystalline cellulose, colloidal silicon dioxide, and saccharin sodium were weighed accurately and then mixed thoroughly by geometric dilution in a clean and dry mortar. The resulting mix was sifted through a sieve No. 60 to make it homogenous after which magnesium stearate was added and uniformly mixed into the blend. The final dry blend was pressured into tablets with 6 mm convex-faced punches on a 16-station rotary tablet compression device. The resultant tablets were then tested with regard to several quality aspects, such as thickness, diameter, hardness, friability, wetting time, water absorption ratio, weight change, uniformity of drug content, uniformity of dispersion, in-vitro dispersion time, in-vitro disintegration time, in-vitro dissolution, moisture uptake, stability, and thermogravimetric/differential thermal analysis (TG/DTA) (Chowrasia P, *et al.*, 2024)

Evaluation of FDT

Vernier calipers were used to determine the thickness and diameter of the formulated tablets and five tablets were randomly picked and the results are expressed in millimeters. The hardness of tablets which is an important parameter that guarantees that the mechanical strength of the tablets during handling and transportation was determined using Monsanto hardness tester, five tablets were determined per batch and the results were expressed in kg/cm². Weight variation test was performed on twenty tablets randomly selected and using single-pan electronic balance (Ax, Shimadzu Corporation, Japan) and the average weight was compared with individual weights as per Indian Pharmacopoeia (I.P.) standards- that not more than two tablets should differ by more than 5 per cent and none by more than twice that value. Friability was determined in a Roche friabilator by weighting twenty tablets ($W_{initial}$), rotating them at 25 rpm during 4 minutes and weighting again (W_{final}) to determine percentage friability. Wetting time, a measure of the disintegration behavior of tablets, and dependent upon both the internal structure of the formulation and the hydrophilicity of excipients, was determined by placing a single tablet on a

double-folded tissue in a Petri dish (6.5 cm diameter) and adding 6 ml of water, and noting the time required to reach complete wetting. Each batch of the material was tested in triplicate, and the values of standard deviation were computed as well (Berardi A, *et al.*, 2022).

The tablets were tested in-vitro disintegration time as per Indian Pharmacopoeia monograph with the help of a tablet disintegration apparatus. The apparatus was loaded with six tablets of each batch of formulation and one liter of disintegration medium was used, which was distilled water. The disintegration time of all the six tablets was noted. In-vitro dissolution tests were carried out by removing 1 ml of dissolution sample at predetermined time points of 1 st, 2 nd, 4 th, 6 th, 8 th and 10 th minute and diluting each to 10 ml with Sorenson buffer (pH 6.8). After each withdrawal, an equal amount of fresh dissolution medium was added to keep the conditions sink. The drug content of every sample was analyzed spectrophotometrically at 231nm against the buffer blank and the average percentage of Lisinopril released at every interval was estimated using the standard calibration curve and plotted against time. The optimized formula, F8 (with 10% Crospovidone), was also submitted to a kinetic analysis in order to determine the drug release mechanism. A graph of log percentage drug remaining against time was plotted and a linear correlation meant that the formulation obeyed first-order kinetics in drug release.

Stability Studies

The optimized formulation F8 (with 10 percent Crospovidone) was subjected to stability studies as per the ICH guideline, to ascertain the shelf-life and integrity of the formulation at different storage conditions. Aluminum foil packing, tightly closed plastic containers, and storage under three conditions namely 4 °C in a refrigerator, 40 °C, 75 relative humidity stability chamber (Oswald, Mumbai), and 60 °C in an incubator were done to the tablets and the study was extended over three months. Samples were removed at 30-day intervals and physical and quality parameters measured, thickness, diameter, hardness, friability, weight variation, drug content uniformity, and disintegration time. Further, in-vitro dissolution testing was conducted at every time point (monthly within 3 months) to check whether there was any alteration in the release profile of the drug throughout the stability period.

RESULTS

Standard Curve of Lisinopril

By UV-Spectroscopy Method

The preformulation investigations were conducted to evaluate the excipient appropriateness and powder blend physical characteristics regarding their tablet formulation. Drug-Excipient compatibility: Compatibility studies indicated that Lisinopril did not exhibit any visible color

change when combined with different excipients namely, crospovidone, croscarmellose sodium, sodium starch glycolate, microcrystalline cellulose, mannitol, magnesium stearate, saccharin sodium and colloidal silicon dioxide, which implies that there is chemical compatibility. All powder mixes had values of angle of repose that fell within acceptable limits thus showing that they have good flow properties. Loss on drying (LOD), affecting tablet manufacture through its effect on excipients susceptible to moisture (e.g., crospovidone, croscarmellose sodium and sodium starch glycolate) was between 1.72 - 2.32%. Colloidal silicon dioxide (Aerosil) was also added to the composition in order to regulate the moisture level. In addition, bulk density and tapped density were determined and based on the results, the Hausner ratio and Carr's Index were computed. The Hausner ratios of all the batches were less than 1.25 and Carr's Index was less than 15%, which is an assurance of the good flowability of the blends. Overall findings of these studies supported the hypothesis that the chosen excipients and powder properties were appropriate to use in direct compression tablet formulation.

➤ Test for Uniformity of Drug Content of Data

In-vitro dissolution tests showed that formulations F1, F2 and F3, which contained Sodium Starch Glycolate (SSG) at the concentration of 5%, 10% and 15% respectively released 92.52%, 95.69 and 97.68% of Lisinopril within 10 minutes. The enhancement of drug release at the elevated level of SSG can be explained by the fact that SSG can rapidly disintegrate and develop fine particle dispersion. Formulations F4, F5 and F6 which incorporated Croscarmellose Sodium (CCS) at 5%, 10% and 15% respectively released 96.21%, 97.67 and 98.33 percent respectively at the end of 10 minutes. It can be speculated that the improved dissolution in the presence of CCS is because of its high swelling ability, which creates hydrodynamic pressure, which enables fast disintegration. Formulations F7, F8 and F9 which incorporated Crospovidone (CP) at 5%, 10% and 15% released the drug at 97.85%, 99.88% and 96.22% respectively at 10 minutes. Although a rise in CP concentration series of 5% to 10% enhanced dissolution, further rise to 15% concentration led to reduced dissolution probably because the pores might have been blocked preventing water penetration. Rapid disintegration and drug dissolution were attributed to the high porous structure of CP up to 10% w/w allowing a quick water uptake. But above this optimum, excessive CP can adversely affect the internal accessibility of water, decreasing the rate of dissolution.

Among the superdisintegrants employed, it was found that the sequence of increasing the dissolution rate was Crospovidone (CP) > Croscarmellose

Sodium (CCS) > Sodium Starch Glycolate (SSG). According to the dissolution profiles and general assessment, formulation F8 that comprised of 10% w/w of Crospovidone was determined as the optimized formulation, with a maximum drug release of 99.88% within 10 minutes. This optimal concentration showed a balance between the fast disintegration and good dissolution rate, which revealed that it is the best among the superdisintegrants tested in this experiment to form mouth-melting tablets (MMTs) of Lisinopril.

Optimized formulation F8 was also tested further by conducting stability studies as per ICH conditions over a period of one month at 40 C / 75% RH in a stability chamber (Osworld, Mumbai), 8 C in a refrigerator and 60 C in an incubator. Physical testing of the tablets was carried out after 15 days interval to determine thickness, diameter, hardness, friability, weight variation, content uniformity, and disintegration time. There were no critical deviations during the term of testing, and all the outcomes were found to be within an acceptable range. Also, in-vitro dissolution tests at time intervals of 15 days performed over a period of one month proved that the release profile of the drug was not affected by

storage at different temperature and humidity levels, which indicated the stability of formulation F8.

➤ **Kinetics of Drug Release**

A optimized formulation F8 upon kinetic treatment releases the drug by first order kinetics.

➤ **First Order Plot**

A graph was then plotted between log cumulative percentage drug remaining vs time. First order kinetics explained formulation F-VII well and the regression value is 0.9025, indicated the drug release dependence on the concentration of the drug.

➤ **Higuchi's Plot**

A graph was also plotted by taking cumulative percentage drug remaining versus square root of time. The regression value is 0.986 which clearly shows that the drug releasing mechanism was highly governed by the diffusion mechanism.

➤ **Korsemeyer Plot**

The plot was done on log cumulative percentage of drug remaining versus log time. n value was 1.9055. This shows that release of drug obeys fickian diffusion.

Table 1: Composition of Fast Dissolving Tablets of Lisinopril

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril	2	2	2	2	2	2	2	2	2
SSG	7	14	21	-	-	-	-	-	-
CCS	-	-	-	7	14	21	-	-	-
CP	-	-	-	-	-	-	7	14	21
MCC	115	108	101	115	108	101	115	108	101
Mannitol	10	10	10	10	10	10	10	10	10
Aerosil	3	3	3	3	3	3	3	3	3
Sodium Saccharin	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Total Weight	142	142	142	142	142	142	142	142	142

Table 2: Evaluation Parameters

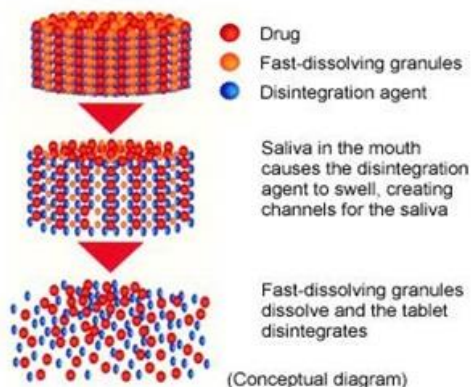
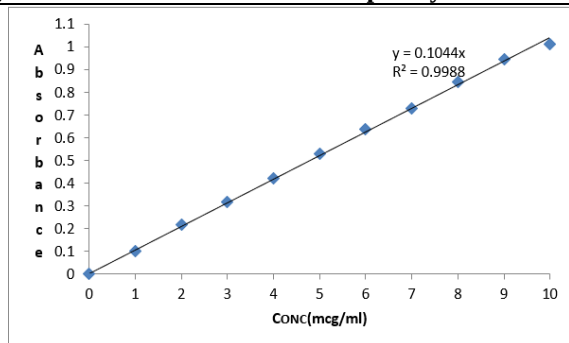
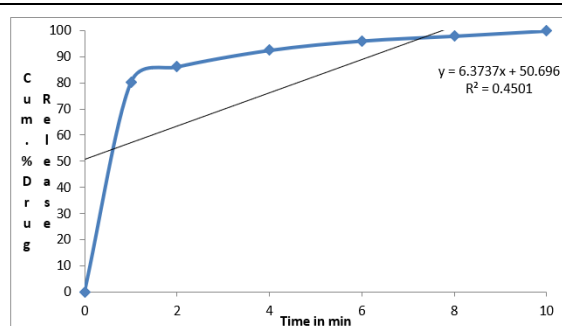
Formulation	Thickness	Diameter	Hardness	Friability (%)	Weight Variation
F1	3.11±0.04	7.94±0.11	3.86±0.12	0.381	139.55±0.13
F2	3.13±0.13	8.03±0.12	3.89±0.14	0.372	139.75±0.98
F3	3.14±0.06	7.96±0.06	3.92±0.19	0.366	139.65±0.89
F4	3.18±0.09	8.13±0.09	3.86±0.17	0.387	140.85±0.62
F5	3.15±0.12	8.02±0.17	3.84±0.09	0.343	139.30±1.08
F6	3.17±0.14	7.89±0.21	3.81±0.21	0.361	139.10±0.48
F7	3.18±0.12	7.92±0.28	3.95±0.16	0.368	139.60±0.67
F8	3.21±0.32	7.94±0.14	3.91±0.11	0.438	139.85±0.38
F9	3.22±0.08	8.02±0.26	3.95±0.13	0.421	139.60±0.64

Table 3: Wetting Time and Water Absorption Ratio

Formulation	Wetting Time	Water Absorption Ratio	Residue remaining on screen	Result
F1	13.12±0.23	78.56	NIL	PASS
F2	13.43±0.32	79.13	NIL	PASS
F3	13.32±0.27	81.02	NIL	PASS
F4	11.17±0.05	76.05	NIL	PASS
F5	11.14±0.02	75.39	NIL	PASS
F6	11.12±0.03	75.22	NIL	PASS
F7	9.8±0.01	69.41	NIL	PASS
F8	9.84±0.15	70.13	NIL	PASS
F9	9.76±0.01	69.56	NIL	PASS

Table 4: Test for Uniformity of Drug Content of Data

Formulation	Drug Content	Residue remaining on screen
F1	99.98±0.69	NIL
F2	99.98±0.071	NIL
F3	100.01±0.13	NIL
F4	100.01±0.21	NIL
F5	100.01±0.18	NIL
F6	100.0±0.081	NIL
F7	99.99±0.037	NIL
F8	99.99±0.068	NIL
F9	100.01±0.037	NIL

Figure 1: Common disk-shaped tablets**Figure 2: Fast dissolving tablets****Figure 3: Standard Curve of Lisinopril by UV – Method****Figure 4: Zero Order Plot**

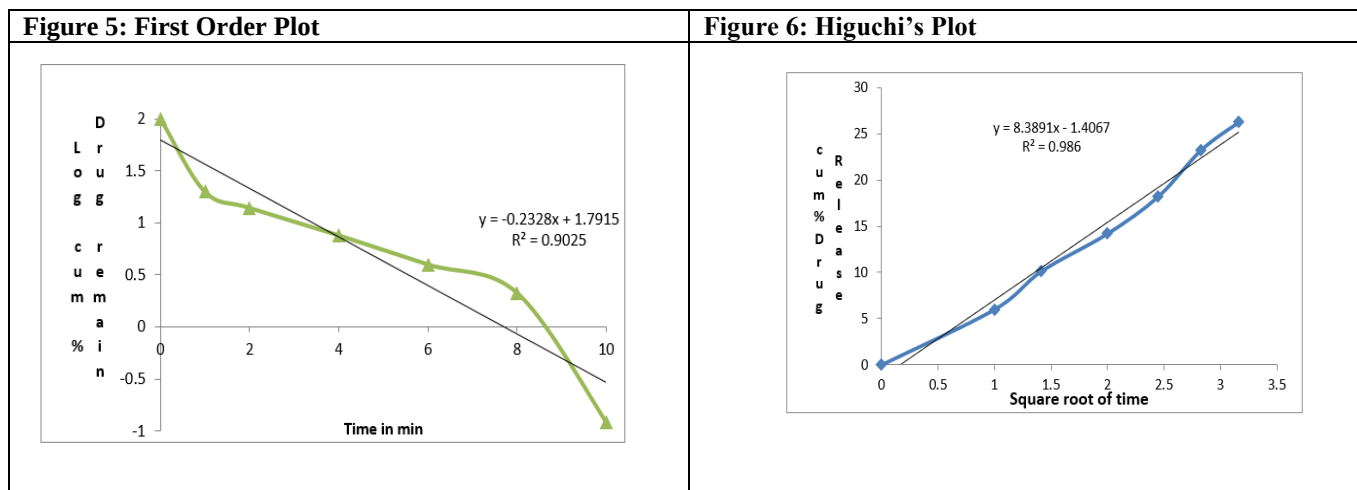
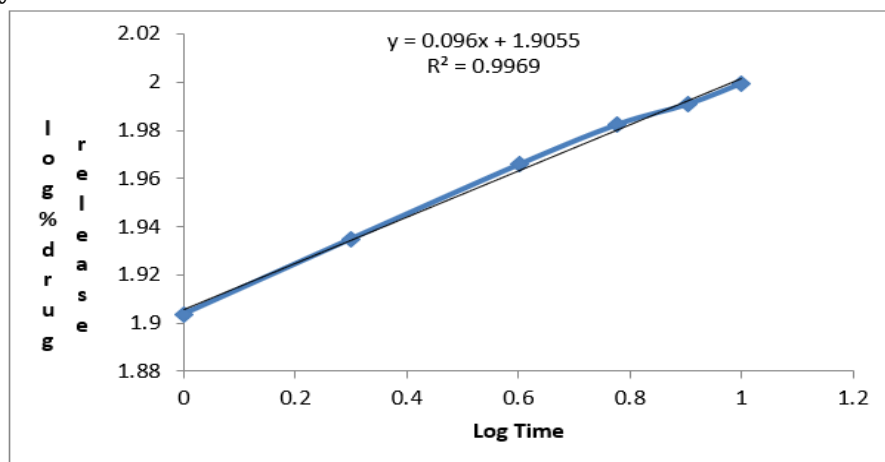


Figure 7: Korsemeyer Plot.



DISCUSSION

Dolasetron fast-dissolving films (FDFs) formulation has been tested in regard to several parameters such as drug content, rate of dissolution, physical properties, and stability, which are critical to the determination of quality and efficacy of the final product. The solvent casting technique was adopted in the formulation in which Hydroxypropyl Methylcellulose (HPMC) and Gellan Gum were employed as film-forming agents, and different excipients, such as citric acid, sodium starch glycolate, and mannitol were added with the aim of optimizing the drug release profile. The percentage drug content of the formulations F1 to F9 was found to be 82.02% to 100.01% and this shows that there is a good consistency in the preparation of the fast-dissolving films (Dhar P, et al., 2020). The difference in drug content is acceptable which proves that the process is reproducible and reliable. Percent yield of the formulations also fell within 84.12-93.4 percent, showing a high recovery of the drug and excipients in the formulation process. Increased yield in formulations F3 and F6 could be due to the fact that these formulations

entrap more drug due to the higher concentration of excipients such as sodium starch glycolate (SSG) and croscarmellose sodium (CCS), hence higher yield. In-vitro dissolution test revealed that formulations F1 to F3, containing F1 having higher percentage of Sodium Starch Glycolate (SSG), displayed greater rate of drug release. Formulation F3 with 15% SSG disintegrated 97.68% of the drug within 10 minutes implying that higher concentration of SSG promotes faster disintegration and easy release of the drug. Likewise, formulations F4 to F6, which had more percentages of croscarmellose sodium (CCS), had a higher dissolution rate, with formulation F6 having 98.33 percent release within 10 minutes (Rahman SN et al., 2020). This is due to the high swelling power of CCS that causes hydrodynamic pressure resulting in an increase in the rate of disintegration and release of drug. A significant increase in the drug release was also observed in formulations F7 to F9 which included Polyplasdone XL (CP) as a superdisintegrant. The drug release in terms of percent was found to increase with concentration of CP up to 10 percent whereafter the release was found to reduce probably because of

blockage of pores within the tablet matrix. The highest percent drug release was seen to be 99.88 percent in optimum concentration of CP in F8 and this was regarded to be the most effective formulation in terms of rapid drug release. The release of the drug loaded in the optimized formulation F8 obeyed first-order kinetics as the first-order plot showed a linear relationship (regression value of 0.9025). This implies that, the drug release rate is concentration dependent and can be modeled using the exponential decay model. Higuchi plot with a regression value of 0.986 indicated that the release of drug F8 is mainly controlled by diffusion mechanism since the release rate grows with time. Korsmeyer-Peppas plot also revealed that the release mechanism is Fickian diffusion as the value of n is equal to 1.9055. This is the typical characteristic of drug release mechanism by hydrophilic matrices whereby the drug release is dependent on the diffusion of water into the matrix which causes the matrix to swell and hence release the drug (Maderuelo C *et al.*, 2011). The optimized formula F8 (containing 10% CP) was subject to stability tests at various conditions (40 °C, 75% RH and 8 °C) and revealed little or no changes in physical appearance, drug content and rate of dissolution even after one month. Stability of F8 formulation at accelerated storage conditions (40 °C, 75% RH) demonstrates that the product

is expected to be stable on its shelf-life. There was also no significant change in the pH, thickness, diameter, hardness, friability, and drug content, which additionally establishes that the formulation is stable over time. F8 is also stable under different environmental conditions despite difference in storage conditions, indicating that it is a stable formulation.

CONCLUSION

Finally, Dolasetron fast-dissolving films have been optimized in terms of the use of different superdisintegrants namely, SSG, CCS, and CP. The optimized formula (F8), which had 10% CP, exhibited amazing dissolution efficiency, drug content, and stability. The release of the drug was associated with the first-order kinetics, and the major mechanism of the release was the diffusion. The stability studies results indicate the possibility of the long-term storage and use of the formulation. The data indicate that Dolasetron FDFs represent an attractive alternative to the traditional dosage forms as they have better bioavailability, faster action onset and are better tolerated by the patients. Additional research, such as clinical trials, should be done to confirm the in-vivo efficacy and safety of the optimized formulation.

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