RESEARCH ARTICLE

Formulation Development and Evaluation of Montelukast Sodium Paper Tablets for Enhanced Drug Release

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ABSTRACT

In this study, the technique of paper-based tablets was evaluated for solubility enhancement of montelukast sodium (MS), an anti-asthmatic, Biopharmaceutical Classification System (BCS) class II medication. Initially, the potential for compressing regular paper into tablets was rigorously examined. Results demonstrated that paper may be utilised to make tablets, regardless of type of the paper utilized. The medicinal quality was satisfactory; and entire tablets of the batch met the Indian Pharmacopeia's criteria. Compressing drug-loaded paper resulted in the formation of drug-loaded tablets. The MS loaded tablets prepared using kitchen roll paper delivered the best results. The tablet was disintegrated in 27 seconds, and drug release of MS was enhanced by 1.88 folds. The tablets were sufficiently hard, and they did not get broken during friability studies. Also, the tablets passed the other evaluation parameters. These paper tablets were also stable under accelerated storage conditions.

Keywords: Montelukast sodium, Paper tablets, Solubility, Disintegration, *In-vitro* dissolution.

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INTRODUCTION

The most effective drug delivery method is *via* oral route, since it is simple to administer, highly stable, has higher patient compliance, is less expensive, and is simple to make.[1] Therefore, the majority of active pharmaceutical ingredients (API) is provided in an oral dosage, and the majority of the new oral formulations have been prepared by pharmaceutical corporations. Today's novel chemical entities (NCE) are generally poorly soluble. To improve the solubility of these NCEs, complex drug delivery systems are required like cyclodextrins, co-crystals formation, micellar preparations, solid dispersion, micronization, nanonization, and co-solvency to name a few.[2]

In recent times, a new medication delivery method was developed to address poor solubility of active pharmaceutical ingredients. The so-called SmartFilm® technology loads amorphous APIs onto a matrix made of regular paper. The weakly water-soluble APIs can be dissolved in a solvent to create SmartFilms®, which can then be added to commercially available paper like a, kitchen towel, disposable handkerchief, cosmetic facial tissues, or washing paper.[3] When compared to bulk material, the paper holds the API in an amorphous state after drying, which improves the API's solubility and dissolving rate. This innovative, straightforward technology is therefore hopeful method for successfully forming ill soluble drugs into an oral drug carrier system.[4]

The ingestion of paper, on the other hand, may not be practicable for the client or person. To increase adoption of the revolutionary technology, SmartFilms® must be compressed in a relatively easy oral dosage form. The paper can be put in the hard gelatin capsules as one alternative.[3] Big-sized pieces of the paper, however, could not be adjusted in body of capsules, therefore, attempts were made to compress the paper into tablets. Initial findings have demonstrated that the paper can be punched into dosage forms, tablets even without the incorporation addition of additional inactive ingredients. After the systematic investigations by Stumpf *et al*., it has been deduced that the tablets prepared using paper denote an innovative, hopeful drug carrier system for effective transport of poor aqueous soluble APIs.[5]

Montelukast sodium (MS) is commonly employed anti-asthmatic drug which can also be used to treat chronic obstructive pulmonary disease (COPD) as well as allergic bronchopulmonary aspergillosis. The chemical active can dramatically enhance the patients' lung function by inhibiting the cysteinyl-leukotriene 1 receptors. Currently, montelukast sodium is available in three different dosage formulations: chewable tablets, pills, and granules.[6] Nonetheless, despite their

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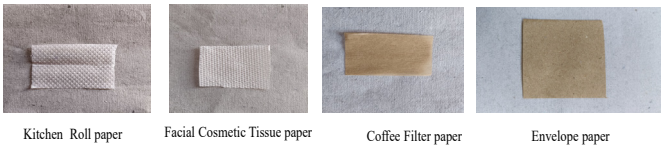

Figure 1: Digital images of different types of papers used for paper tablet preparation

established efficacy, MS formulations have certain limits in their use, including the molecule's inadequate water solubility (100–1000 mg/mL), and its wavering stability to humidity, temperature, and light.[7] Hence, the current investigation aims to develop the paper tablets of a poorly soluble drug, montelukast sodium.

MATERIALS AND METHODS

Materials

Montelukast sodium salt was procured from Aarti Scientific Company, Solapur, Maharashtra, India. Sodium lauryl sulfate was procured from Ozone International, Mumbai, India; ethanol was purchased from Molychem Industries Pte Ltd, Mumbai, India. The envelop paper, kitchen roll paper, facial tissue, and coffee filter paper were purchased from the local market.

Methods

Estimation of Montelukast sodium by UV spectrophotometric analysis

In this work, MS was estimated using a UV spectrophotometric method at the wavelength of absorption of 340 nm.

Standard curve preparation for montelukast sodium

In order to prepare a stock solution of a concentration 1-mg/mL, 10 mg MS was precisely taken and added to a 10 mL volumetric flask and then dissolved in a minimum amount of ethanol. Distilled water was then used to further dilute the stock solution. Working solutions of concentration 10 to 50 µg/mL were made from stock solution by serial dilution with water. The absorbance of prepared solutions was then measured using an ultraviolet-visible spectrophotometer at 340 nm. The absorbance was then plotted against MS concentration to prepare the standard curve.

Paper sterilization

Papers of all grades, including envelop paper, kitchen roll paper, facial tissue, and coffee filter paper, were sterilized by heating them in a hot air oven for 10 minutes at temperatures between 150 and 200°C. The sterilized papers were then used for the subsequent procedures.[8] The digital images of all types of papers are depicted in Figure 1.

Manufacturing of drug-unloaded tablets

In the initial section of investigation, single punch tablet press (Rimek, India) was used to manufacture unloaded round-shaped tablets with a diameter of 10 mm and weight of around 200 mg at a compression force of about 30 kN. The various varieties of paper were divided into fragments. These fragments, each with a weight of around 200 mg, prior to compression.[5] Analysing the corresponding mass/volume allowed for an approximate determination of the paper's density (Figure 2).

In order to manage the mass, the appropriate paper area was determined, cut, and measured for weight. Paper sheets were then divided into pieces that were around 1 × 1 cm in size. The tablet press's cavity was then manually filled with the resulting tiny bits of paper, which were manually compressed.[5] The tests given in the Indian Pharmacopeia for tablets were carried out to assess the qualities of the tablet dosage forms produced.[9]

Manufacturing of API-loaded tablets

The preparation of drug-filled tablets was the goal of the study's second section. The manufacturing process is summarised in Figure 3. First, paper with a mass of 200 mg was divided into sheets. Using a pipette, montelukast sodium salt solution (20 mg/mL) was added to the sheets to fill them with the drug. Thus, the sheet acted as a matrix. After drying, the process was repeated, resulting in a total montelukast sodium salt dosage of 10 mg per sheet of paper. The sheets were divided into tiny pieces, each measuring roughly 1 X 1 cm. The drug-laden paper fragments were again inserted into the tablet press's hollow by hand and compressed manually. Subsequently, the characteristics of the tablets loaded with the drug were evaluated. Furthermore, an examination of content consistency and drug release was carried out in accordance with the Indian Pharmacopeia guidelines.[9]

The montelukast sodium was loaded in different types of matrices, i.e., different types of papers, using the described method. Such prepared formulations were coded as F1, F2, F3, and F4. Table 1 displays the formulation of paper tablets manufactured for selection of suitable paper for MS loading.

All these prepared tablets were evaluated according to the Indian Pharmacopoeia 8.0. Based on the results obtained, two papers were selected for further optimization studies in which the quantity of paper matrix was varied. Table 2 displays the formulations of tablets used for optimization studies.

Evaluation of paper tablets

- *Mass uniformity*

As per test method of the Indian Pharmacopeia, mass uniformity was conducted. Twenty tablets were chosen at random and weighed. The average weight was then computed, and each mass's percentage deviation was calculated. The

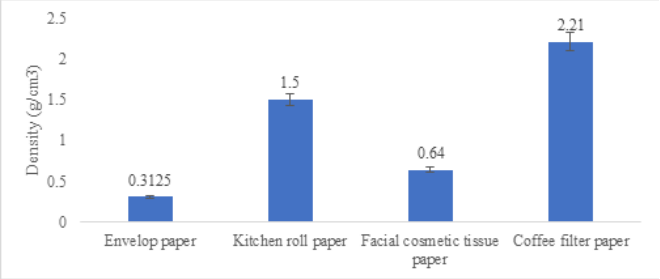

Figure 2: Density of a variety of paper utilized for the manufacturing of paper tablets

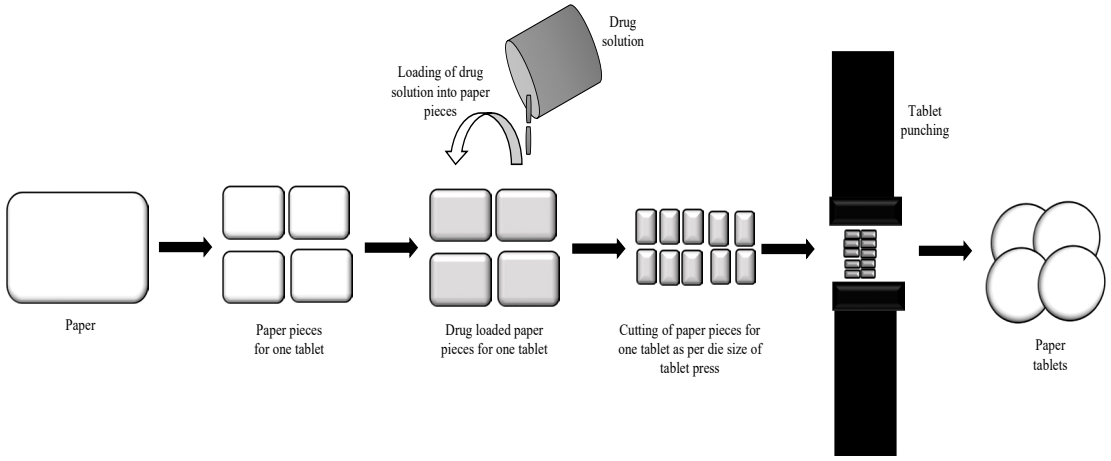

Figure 3: Manufacturing scheme for preparation of MS-loaded tablets

outcomes were compared with the values given in Indian Pharmacopeia.[9]

- *Content uniformity*

According to test method given in the Indian Pharmacopeia, content uniformity was examined for the MS-loaded tablets. Drug content was assessed by ultraviolet-visible spectroscopy (Schimadzu, Japan) at 340 nm on a total of 10 randomly chosen tablets. If the content of each individual tablet ranged from 85 to 115% of the average content, the preparation complied with the standards.[9]

- *Resistance to tablet crushing*

Resistance to tablet crushing was tested using test method from the Indian Pharmacopeia. A hardness tester (Monsanto, India) was used to determine the hardness of tablets (n = 10). The tablets were clamped between the jaws and the force needed to break the tablet was determined. The average hardness with standard deviations is used to express the results.[9]

- *Friability*

The friability with an abrasion drum was utilized, and the Indian Pharmacopeia's test method was used to measure the friability of tablets (Roche, India). The quantity of paper tablets used for this procedure was about 6.5 g. Prepared paper tablets were meticulously dedusted and cleaned before testing. The sample tablet's weight was accurately calculated. The drum was then filled with tablets and rotated 100 times at 25 rpm. Tablets were then taken out, dedusted, and precisely weighed. A weight loss of under 1.0% was considered permissible as the maximum allowable limit. The weight loss (percent) was determined.[9]

- *Disintegration*

Tablets (n = 6) were used in the investigation of the paper tablet's disintegration in water. The manufactured paper tablets were independently inserted into the disintegration tester's voids (Veego, India), and the time it took for the tablets to disintegrate was recorded as they were subjected to vertical movement at a frequency of 29 to 32 movements per minute, within a range of 50 to 60 mm. The temperature maintained during the test was 37 ± 2°C. If tablets broke down within 15 minutes, the results were deemed acceptable.

Table 1: Formulation table of paper tablet preparation for preliminary studies of paper selection

Ingredients	*F1*	*F2*	*F3*	*F4*
MS (mg)	10	10	10	10
Ethanol (mL)	0.1	0.1	0.1	0.1
Envelop paper (mg)	200	-	-	-
Kitchen roll paper (mg)	-	200	-	-
Facial tissue paper (mg)	-	-	200	-
Coffee filter paper (mg)	-	-	-	200
Total (mg)	210	210	210	210

Table 2: Formulation table for optimization studies of envelope paper and kitchen roll paper

Ingredients	O1	O2	O3	O4
MS (mg)	10	10	10	10
Ethanol (mL)	0.1	0.1	0.1	0.1
Envelop paper (mg)	300	400	-	-
Kitchen roll paper (mg)	-	-	300	400
Total (mg)	310	410	310	410

- *Dissolution*

According to test method of the Indian Pharmacopeial standard, a dissolution study was conducted using MS-incorporated tablets (Electrolab, India). This study was conducted by adding a tablet in each vessel that contained 900 mL of 0.5% w/v SLS in distilled water as a dissolution medium and was maintained at a standard temperature of 37 ± 0.5°C (n = 6). The paddle apparatus was rotated at 100 rpm speed. The dissolution aliquots were collected at time intervals of 0, 2, 5, 10, 20, and 30 minutes, and dissolution media was replaced to persist the sink conditions. Each of these samples was filtered through a filter featuring a pore diameter of 0.22 micrometers and

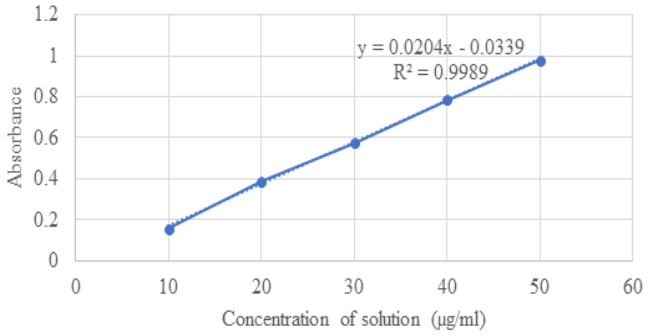

Figure 4: Calibration curve of montelukast sodium in distilled water

subsequently analyzed using UV spectroscopy (Shimadzu) at 340 nm.[9]

- *Stability study of prepared formulations*

All the prepared tablets were stored in a stability chamber for 3 months duration under accelerated storage settings of 45°C temperature with a relative humidity of 75%.[10]

RESULTS AND DISCUSSION

Estimation of Montelukast Sodium by UV Spectrophotometric Analysis

The investigational drug, MS exhibited the wavelength of maximum absorption at 340 nm. A standard curve of MS was prepared in distilled water, and it showed linearity within the concentration range spanning from 10 to 50 µg/mL. A prepared calibration curve is shown in Figure 4.

Manufacture and Evaluation of Unloaded Tablets

Figure 5 displays representative pictures of the tablets made from the four various kinds of papers. The pictures show that it is feasible to compress regular paper, regardless of the kind that is employed. Each tablet has a smooth surface and resembles traditional uncoated tablets in appearance. Table 3 provides a summary of the evaluation tests.

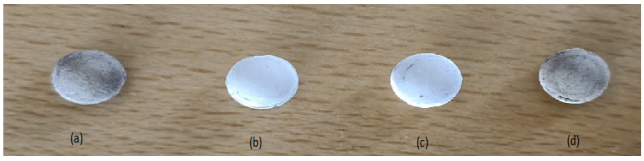

Figure 5: Images of unloaded paper tablets (a) Envelop paper, (b) Kitchen roll paper, (c) Facial tissue paper, (d) Coffee filter paper

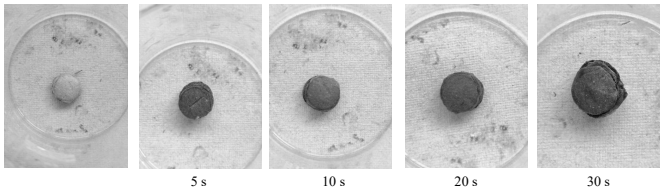

Figure 6: Disintegration and disaggregation of envelope paper tablets in first 30s (images were captured within a beaker without any agitation or stirring conducted)

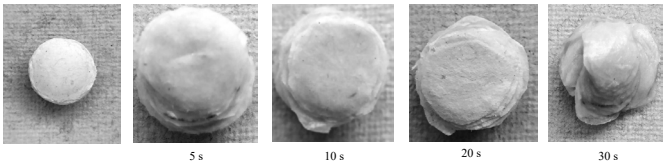

Figure 7: Disintegration and disaggregation of kitchen roll paper tablets in first 30s (images were captured within a beaker without any agitation or stirring conducted.)

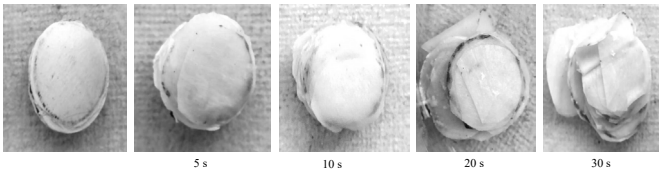

Figure 8: Disintegration and disaggregation of facial tissue cosmetic paper tablets in first 30s (images were captured within a beaker without any agitation or stirring conducted.)

Results show that every tablet met the requirements set forth by the European Pharmacopeia. Disintegration was accomplished within the three minutes. Within five seconds, the tablets began to expand dramatically and initiated to disintegrate. The tablet's volume doubled after 10 seconds and tripled within 20 seconds. The tablet crumbled after 30 seconds, leaving all the paper wet and pliable (Figures 6-8). After about a minute, all of the little pieces of paper had disintegrated.

Manufacture and Evaluation of MS-incorporated Paper Tablets

The initial phase of the research demonstrated that tablets could be manufactured from standard paper, regardless of the paper's composition. In the subsequent stage, the objective was to explore the possibility of preparing medication-loaded tablets using paper, and how the release profile of the MS is enhanced depending on the type of paper.

Various types of paper were permeated with MS, and the resultant paper-based drug-loaded films were subsequently cut into small segments and compressed following the previously mentioned procedure. The pharmaceutical evaluation of these tablets is presented in Table 4, and the release patterns of MS are depicted in Figure 9. The dissolution process of paper tablet can be visualized from Figure 10.

The findings indicated that medication-loaded paper could be effectively compressed into tablets. Much like the tablets without medication, the drug-containing tablets, regardless of the paper variety employed, exhibited suitable pharmaceutical attributes. Consequently, all tablets, irrespective of the paper employed as a matrix, met the necessary criteria outlined in the Indian Pharmacopeia (refer to Table 4).

The tablets' exteriors looked to be bright and smooth. The distinct sheets of paper remnants various could be seen on some of the tablets, though. The release of MS in the designated dissolution media is found to be less, with a mere release of 46.54%. The tablets with MS that were manufactured from envelope paper (F1) showed 73% drug release, while the API release of 86.4% was achieved with kitchen roll paper (F2).

Table 3: Post-compression parameters of paper tablets

Formulation no.	*Thickness (cm)*	*Avg wt ± SD (mg)*	*Hardness (g)*	*Friability*	*Avg. DT (sec)*	*Content uniformity (%)*
Envelope paper	0.4	193.2 ± 0.0056	2.33	0.08	170	91.36 ± 0.9
Kitchen roll paper	0.4	213.11 ± 0.0076	0.266	0.27	31	97.25 ± 0.58
Facial tissue paper	0.4	214.68 ± 0.0036	0.333	0.21	45	95.33 ± 0.69
Coffee filter paper	0.4	205.78 ± 0.0011	0.251	0.39	22	94.26 ± 0.54

Table 4: Post-compression parameters of paper tablets (Selection of paper)

Formulation no.	*Thickness (cm)*	*Avg wt ± SD (mg)*	*Hardness (g)*	*Friability*	*Avg. DT (sec)*	*Content uniformity (%)*
F1 (Envelope paper)	0.4	194.2 ± 0.0017	2.25	0.10	155	96.32 ± 0.59
F2 (Kitchen roll paper)	0.4	195.11 ± 0.0045	0.269	0.36	37	99.52 ± 0.12
F3 (Facial tissue paper)	0.4	202.68 ± 0.0069	0.310	0.25	52	92.24 ± 0.69
F4 (Coffee filter paper)	0.4	215.78 ± 0.0044	0.266	0.48	23	94.60 ± 0.85

Also, the formulations F3, and F4 released 64.79, and 59.14% drug, respectively at the last time point in dissolution studies. All the formulations were found to enhance the release of MS compared to the powdered form. The matrix of papers was found to enhance the release profiles in the order kitchen roll paper > envelope paper > facial cosmetic tissue paper > coffee filter paper. These variations could be associated with the distinct characteristics of the various types of papers, like paper wettability, density, porosity, grain number, and strength. The interaction and placement of the API within the paper also play a role in the disparities observed in the release pattern. In line with the SmartFilm® theory, the API can be incorporated into the paper's pores, where it either adheres on a molecular level or fails to crystallize because of the paper's small pore sizes. Consequently, this results in a more rapid drug release compared to crystalline materials.[3,4] The physicochemical characteristics of the papers and the API's crystallinity were not examined in this investigation. As a result, this set of data cannot be used to evaluate how the paper's structure and/or the active substance's crystalline state affects drug release.

However, a distinction between the various paper tablets' resistance to crushing was revealed, as shown in Table 3. Tablets formulated from envelope paper exhibited notably

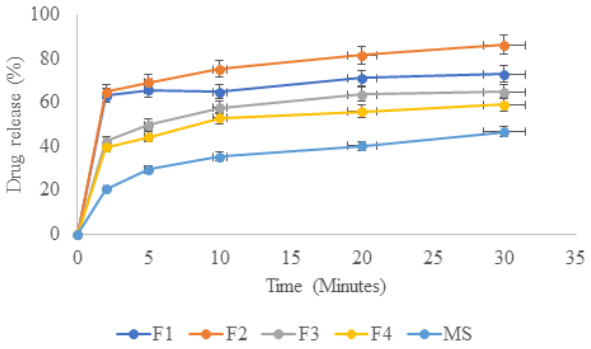

Figure 9: Dissolution studies of formulations F1, F2, F3, and F4 for selection of paper for MS

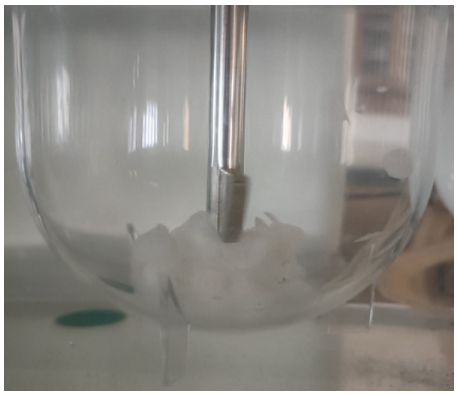

Figure 10: Paper tablets in completely disintegrated form (image captured using a paddle apparatus at 50 rpm)

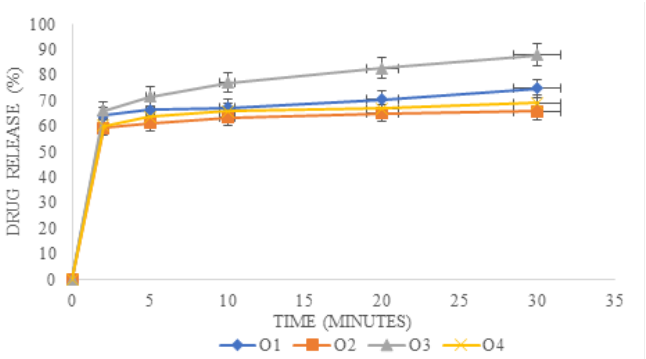

Figure 11: Dissolution studies for optimization of paperweight

greater resistance to compression, measuring approximately 2.25 grams, compared to facial tissue, kitchen roll, and coffee filter paper. Concomitant results were obtained in friability testing. Also, the manufactured paper tablets were sufficiently hard, as not a piece of paper separated during the friability studies. In addition, all the drug-loaded tablets passed the weight uniformity as well as content uniformity criteria of European Pharmacopoeia.

Table 5: Post-compression parameters of paper tablets for optimization of paper weight

Formulation no.	*Thickness (cm)*	*Avg wt ± SD (mg)*	*Hardness (g)*	*Friability*	*Avg. DT (sec)*	*Content uniformity (%)*
O1	0.45	317.21 ± 0.0029	2.12	0.10	164	91.22 ± 0.16
O2	0.49	409.19 ± 0.0016	2.03	0.20	152	90.04 ± 0.39
O3	0.47	302.17 ± 0.0093	0.249	0.33	27	98.12 ± 0.19
O4	0.51	412.19 ± 0.0092	0.231	0.41	21	102.63 ± 0.09

Table 6: Dissolution profile of formulations after stability studies

Time (Minutes)	*%Drug release*			
	F1	*F2*	*F3*	*F4*
0	0	0	0	0
2	63.35	64.84	42.31	39.55
5	65.77	69.35	49.94	44.27
10	66.85	75.32	57.61	52.84
20	71.14	81.55	63.86	55.95
30	73	86.4	64.79	59.14

Table 7: Dissolution profile of optimized formulations after stability studies

Time (Minutes)	*%Drug release*			
	O1	*O2*	*O3*	*O4*
0	0	0	0	0
2	64.26	59.32	65.96	60.15
5	66.33	61.09	71.58	63.69
10	67.27	63.25	76.95	65.84
20	70.36	64.87	82.61	66.95
30	74.66	65.82	86.35	68.95

As the envelop paper, and kitchen roll paper produced the tablets with higher drug release, the effect of their amount in the formulation on the characteristics of produced paper tablets was evaluated. And, accordingly formulations O1, O2, O3, and O4 were manufactured. The post-compression parameters of these paper tablets were then evaluated (Table 5).

From Table 5, it is obvious that the enhancement in paper weight caused a reduction in the tablet hardness, which ultimately resulted in reducing the disintegration time. The effect of the amount of paper on drug release is depicted in Figure 11. It is evident from the drug release profile that an increase in paper amount in tablet formulation resulted in enhanced drug release, however, only up to a certain limit. The use of 300 mg of paper in formulations O1, and O3 resulted in enhanced drug release. However, the drug release was retarded when the amount of paper in the formulation was further increased to 400 mg. Thus, it can be stated that the usage of significantly higher amounts of paper in the formulation retards the drug release, which can be ascribed to the formation of a diffusion layer of a higher thickness during the drug dissolution process. Another reason for retarded drug dissolution can be explained by the fact that the drug might get again entangled in the higher amounts of a paper matrix, which had got segregated during the disintegration and dissolution process. The process can be visualized in Figure 10.

Altogether, among the studied formulations, the formula O3 produced outstanding results with a disintegration time of 27 seconds and a drug release of 87.91%, which is 1.88 times greater than the powdered MS.

Stability Studies

The tablets manufactured using all kinds of papers were subjected for stability testing, and changes are absent after storage. The content of drug was discovered to be consistent. Drug release data are provided in Tables 6, and 7. From the data, it can be stated that, even after storage at 40°C, there are no appreciable deviations in drug release. The product's gradual drug release properties are found to be stable and unmodified.

CONCLUSION

Montelukast sodium a highly effective anti-asthmatic medication, is a leukotriene receptor antagonist. This medication belongs to BCS class II, which denotes that it has a high permeability and poor solubility. Formulation of MS in the paper tablet, therefore provided the solubility benefits. The technology doesn't contain excipients and uses a co-solvency approach to make the medicine more soluble while improving drug release. The paper tablet was made using the co-solvency technique and contained the medicine together with various types of paper like envelope paper, kitchen roll paper, cosmetic facial tissue, and coffee filter paper. The examined results support the claim that the developed formulation's performances are satisfactory. The MS in the kitchen roll paper type tablet releases 89.91% of the drug in 30 minutes, which is the best release of all the formulations. The O3 is found to be an ideal formulation because additional properties, including hardness, friability, weight fluctuation, and thickness, are within the limits. The stability of the tablets is also attained. In sum, paper tablets are found to be one of the effective strategies for oral delivery of poorly soluble pharmaceutical actives.

AUTHORS CONTRIBUTIONS

Each author made an equal contribution.

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