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ORIGINAL ARTICLE

Formulation and Characterization of Sublingual Tablets of Iloperidone Prepared by Microenvironmental pH Regulated Approach

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Abstract

Purpose Iloperidone (Ilo) is an antipsychotic drug having low and pH-dependent solubility, hence less bioavailability. Thus, the aim of this study was to prepare and characterize binary (TAPOL B) and ternary complexes (TAPOL T) of drug with Kolliphor P-188 and tartaric acid to improve solubility. Further, sublingual tablets incorporating ternary complex were formulated to improve the dissolution.

Methods Preliminary screening studies were conducted to select the acidifying agent and polymer based on saturation solubility studies. Binary and ternary complexes were prepared by the melting method. Complexes were characterized by DSC, powder X-ray diffraction (PXRD), FTIR, microenvironmental studies, and in vitro dissolution studies. The sublingual tablets of ternary complexes were prepared by the direct compression method and evaluated for weight variation, disintegration time, and dissolution studies.

Results Based on solubility studies, Kolliphor P-188 and tartaric acid were selected as polymer and acidifying agents. DSC studies and FTIR spectra showed the interaction of drugs with polymer and acidifying agents. PXRD spectra showed the crystalline nature of complexes. Microenvironmental studies carried out in pH 6.8 showed a drastic decrease in pH with ternary complex as compared with binary complex. Dissolution studies showed an increase in dissolution, TAPOL T > TAPOL B > drug. The sublingual tablets showed disintegration time < 30 s and more than 80% of a drug released within 10 min. Due to the presence of tartaric acid and polymer, solubility of the drug increases tremendously.

Conclusion The present study demonstrates the increase in solubility and release of Iloperidone due to the microenvironmental pH effect from sublingual tablets. Hence, microenvironmental pH modification is a good approach to increase drug solubility and dissolution.

Keywords Iloperidone · Tartaric acid · Kolliphor P-188 · Ternary complex · Microenvironmental pH · Sublingual tablets

Highlights
- Binary and ternary complexes of Ilo were formulated.
- Kolliphor P-188 and tartaric acid were optimized as a polymer and an auxiliary agent.
- Tartaric acid accelerated the dissolution efficiency of the drug due to pH change.
- DC tablets showed ≥ 80% release within 5 min for 12 mg, maximum strength.

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Introduction

Iloperidone (Ilo) is a second-generation antipsychotic drug approved by USFDA in May 2009 [1]. Ilo belongs to the chemical class of piperidinyl-benzisoxazole derivatives and acts as a dopamine D2 and 5-HT2A receptor antagonist and as a neuroleptic agent. Ilo is used widely due to its potent nature which signifies the desired activity at lower doses (12–16 mg). Ilo tablets are available in the market in different strengths like 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. Ilo has several benefits compared with other antipsychotic drugs like low affinity for histaminic receptors, minimum risk of sedation, and significant development in extrapyramidal symptoms [2–4]. Ilo is a BCS class II drug; hence, solubility is very low and pH-dependent solubility, thus less bioavailability. Also, it shows high first-pass metabolism [5]. Solubility of Ilo has been enhanced by microspheres, binary, ternary complexation with cyclodextrins, self-emulsifying preconcentrate, whereas bioavailability of Ilo has been improved by co-crystallization, sublingual film, and nanolipid carriers [5–10]. Among them, oral administration is mostly preferred as it advantageous compared with other routes of administration. Delivery of drugs via oral mucous membrane is known to be a potential approach to the oral route of drug delivery. The sublingual route is preferred when a faster onset of action is required along with patient ease. Permeability of the oral cavity can be given in decreasing order as follows: sublingual followed by buccal, followed by palatal. The sublingual route of drug delivery bypasses the hepatic first-pass metabolism leading to desired bioavailability. The drug is absorbed through passive diffusion into the lipoidal membrane, and thus, its absorption is 3–10 folds higher than the conventional oral route [11–13].

Schizophrenia is a chronic and severe mental disorder that alters the way a person thinks, feels, and behaves. It disables the patient's ability to socialize and to communicate and express freely. People suffering from schizophrenia behave as if they have a connection with the real world. Antipsychotic drugs given in the form of sublingual tablets are beneficial for patients suffering from these types of syndromes as they provide better patient compliance. Idiosynchronies in the behavior of patients are also well managed since the drug can be disguised with an esthetic appearance, sweet taste, and likely flavor which resembles more with a mouth freshener than a medicine [14].

Especially, microenvironmental pH regulated formulation can be a good strategy. While binary complexes demonstrated an enhancement in solubility and dissolution of poorly soluble drugs, a supplement of auxiliary agent, i.e., pH modifier forms ternary phase, has proven further enhancement in solubility and dissolution. The system with the microenvironmental pH approach has successfully resolved the issues of pH-dependent solubility for some drugs [13, 15–17].

This work aimed to prepare and characterize binary (TAPOL B) and ternary complexes (TAPOL T) of drug with Kolliphor P-188 and tartaric acid. To formulate sublingual tablets incorporating the ternary complex for improvement in dissolution and thus bioavailability. Complexes were characterized by DSC, powder X-ray diffraction (PXRD), FTIR, microenvironmental studies, and in vitro dissolution studies. The sublingual tablets (strength 12 mg) of ternary complexes were prepared by the direct compression method and evaluate for physical parameters and dissolution studies.

Material and Methods

Materials

Ilo (Symed Labs), Kolliphor P-188 (BASF), and tartaric acid (MolyChem) were obtained as a gift sample. Sodium starch glycolate, magnesium stearate, and Crospovidone have been purchased from MolyChem. Mannitol and microcrystalline cellulose were purchased from S.D. Fine chem. Purified water was used to prepare the solutions. Analytical grade reagents and chemicals were used.

Methods

Preparation of Complexes

Based on solubility studies done by us, Kolliphor P-188 was selected as a polymer, whereas tartaric acid was selected as a pH modifier [8]. Complexes were prepared by the melting method [18–22]. To finalize drug to polymer ratio, Ilo:Kolliphor P-188 was tried in 1:1, 1:2, and 1:3 ratios. The polymer was melted at 60 °C using a hot plate, and the drug was uniformly dispersed in molten mass by stirring. After 5 min, the molten mass was gradually cooled down. Further, the solidified mass was sifted through a sieve (#40). Solubility studies were carried out by adding excess amount complexes in 10 ml of water, shaking on an orbital shaker (Orbitek, Scigenics Biotech, India) at 100 rpm for 24 h. After 24 h, samples were filtered and analyzed by the HPLC method to quantify the drug present [5]. Ternary complexes were prepared using Ilo:Kolliphor P-188:tartaric acid (1:1:0.4) as described above, adding tartaric acid as a pH modifier along with drug in molten mass.

Preparation of Tablets by Direct Compression

The direct compression method was used to manufacture the tablets. Each 100 mg tablet consisted of 25 mg of complex equivalent to 12 mg of Ilo as an API, 8 mg sodium starch glycolate, and crospovidone as a disintegrant respectively, 40 mg of mannitol as a filler and sweetener, 2 mg of magnesium stearate as a lubricant, and 17 mg of microcrystalline cellulose as a filler also acts as a sweetener. The required

quantities were weighed. These ingredients were passed through 60 mesh sieve and mixed for about 15 min to assure uniform blending of the ingredients. The powder was mixed with weighed quantities of magnesium stearate which was previously passed through 100 mesh sieve. The mass was directly compressed in a tablet compression machine (Rimek Minipress, India) using 7 mm of punch (BB Tooling) to form a tablet.

Characterization of Complexes

DSC

The samples of the drug, tartaric acid, Kolliphor P-188, and TAPOL were studied using differential scanning calorimetry (Mettler Toledo). For reference, an empty aluminum plate was used. DSC measurements were achieved at a heating rate of 10 °C/min from 30 to 300 °C.

FTIR

Fourier transform infrared spectroscopy of drug, tartaric acid, Kolliphor P-188, and its complexes was carried out using an FTIR spectrometer (Perkin Elmer) over a range of 4000–400 cm^{-1}. The peaks of complexes were compared with that of the drug, Kolliphor P-188, and auxiliary agent to check the presence of characteristic peaks.

X-ray Diffraction (PXRD)

A D8 advance X-ray diffractometer was utilized to analyze the PXRD pattern of Ilo, polymer, auxiliary agent, and complexes. The samples were examined between 5 and 60 (2θ) by acceleration voltage and current of 45 kV and 40 mA, respectively. The standard peaks and its intensity data were united and evaluated using software Origin 8. The change in characteristic peaks of Ilo and complexes were marked and compared to determine crystalline nature.

In Vitro Analysis

In vitro analysis of API and complexes was conducted using Dissolution Tester USP Type II (Paddle type) (Electorlab, India) in a capsule shell. Phosphate buffer pH of 6.8 (500 ml) was used as dissolution media at 37 ± 0.5 °C and 50 rpm. About 10 ml aliquot of dissolution media was taken at a time interval of 5, 10, 15, 30, 45, and 60 min. Drug release profiles exhibited by the complexes were then compared.

Microenvironmental Studies (MepH)

Complexes were tested to check the effect of MepH and to identify the changed surface features of complexes in various dissolution media. Further, these complexes were positioned in different dissolution media, i.e., buffer pH 1.2 and phosphate buffer pH 6.8 ($n = 3$). Later programmed time intervals, pH was determined using a calibrated pH meter at 5, 10, 15, 30, and 45 min and calculated in contrast to the time [22].

Quality Control Tests of Tablets

Weight Variation

Twenty tablets were selected at random and weighed individually on an electronic balance, and the average weight was calculated. Uniformity of weight should comply with the IP specifications. As per IP 2018, not more than two of the individual weights should deviate from an average weight by more than 10% and none should deviate more than twice the percent [23].

Content Uniformity

Ten tablets were weighed individually and were crushed; then, the drug equivalent to 20 mg was extracted in methanol, and volume was made up to 100 ml with distilled water. Then the solution was filtered and the first 10 ml of the filtrate was discarded. About 1 ml was pipette out from the filtrate and was made up to 10 ml with distilled water. The samples were analyzed using the HPLC method [24].

Hardness

The hardness of ten tablets was determined using Pfizer hardness tester, and the average values were calculated.

Thickness and Diameter

The thickness and diameter of twenty tablets were measured using Vernier caliper, and the average values were calculated.

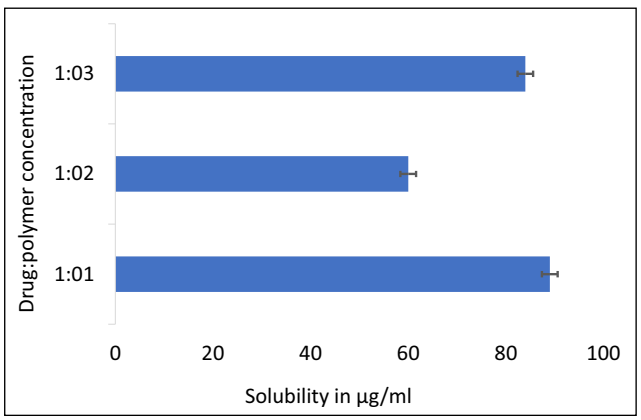

Fig. 1 Solubility of drug in different concentration of Kolliphor P-188 (values are the mean of three determinants (mean ± SD))

Friability

Ten tablets are individually weighed and placed in a plastic chamber which revolves at 25 rpm for 4 min. The tablets were then reweighed, and loss in weight in terms of percentage was found [23]. The friability of tablets was determined by the following formula:

$$Percentage\ Friability = [(Weight\ of\ initial\ tablets - Weight\ of\ final\ tablets)/(Weight\ of\ initial\ tablets)] \times 100$$

Disintegration Test

The disintegration test was performed using the Disintegration Test Apparatus USP. pH 6.8 phosphate buffer was placed in the beaker of the DT apparatus, the temperature was maintained at 37 ± 0.5 °C, and the disintegration time of tablets was noted [22].

In Vitro Drug Release Study

The release rate of sublingual tablets was performed using Dissolution Testing Apparatus II (Paddle type). The in vitro drug release was performed using 500 ml of 6.8 pH phosphate buffer solution maintained at a temperature of 37 ± 0.5 °C for 1 h at 50 rpm. Aliquots 10 ml was withdrawn from the ELECTRO LAB dissolution apparatus at time intervals of 5, 10, 15, 30, 45, and 60 min. The aliquots were filtered through a 0.45-μ membrane filter and diluted to a suitable concentration with buffer and analyzed by HPLC [5].

Result and Discussion

Preparation of Complexes

From solubility studies, Kolliphor P-188 exhibits an increase in the solubility of the drug which is used as a polymer [8]. Tartaric acid was optimized as an auxiliary agent among other acids and bases; 0.4% concentration of tartaric acid showed optimum solubility of the drug [8]. Also, drug and polymer in the ratio of 1:1 showed maximum drug solubility (89.92 ± 1.6 μg/ml; mean ± SD) compared with the other ratio (Fig. 1). Captivatingly, the enhancement in the solubility of Ilo in the presence of tartaric acid was observed similar to our

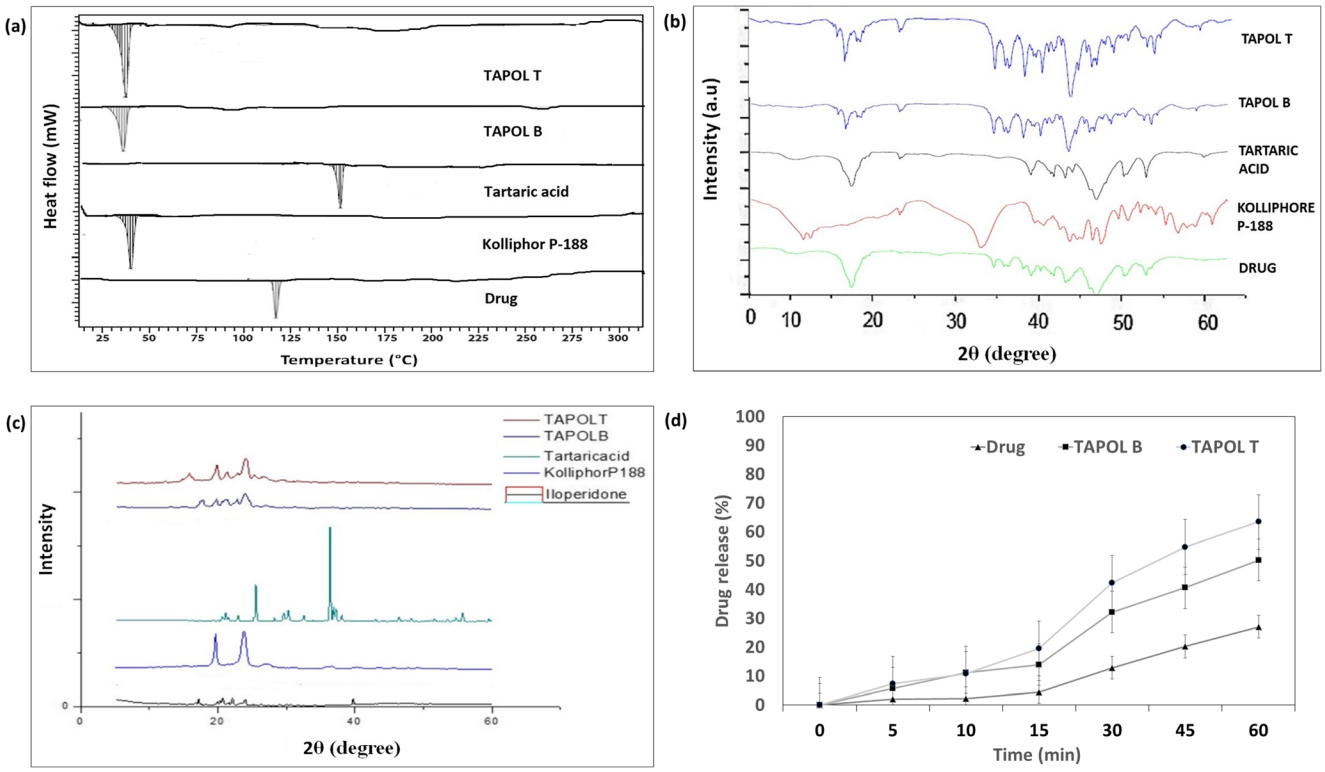

Fig. 2 **a** DSC of drug and complexes and **b** FTIR spectra of drug and complexes, **c** PXRD of drug and complexes, and **d** dissolution of drug and complexes ($n = 3$, mean ± SD)

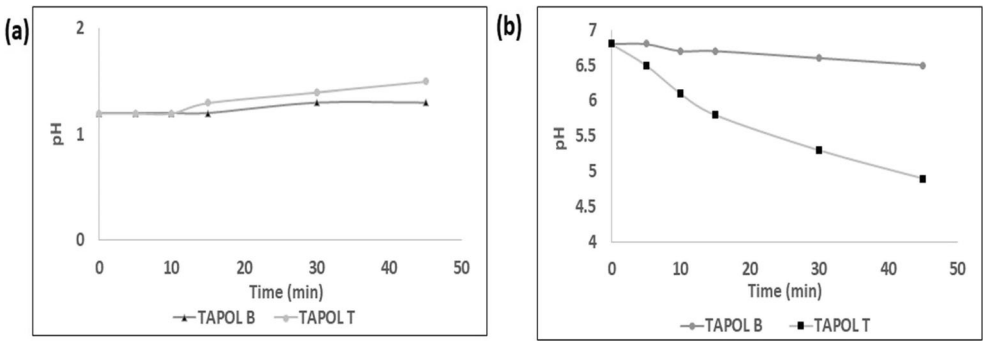

Fig. 3 Microenvironmental pH studies in **a** pH 1.2 and **b** pH 6.8

earlier studies proposed its integration into the binary complex to form a ternary complex [8].

Characterization of Complexes

DSC

The thermal behavior observed by DSC showed an intense and well defined endothermic peak at 120 °C, corresponding to the drug melting point. Hence, it was confirmed as Iloperidone. The glass transition temperature of TAPOL B and T showed a drastic change in the melting point at 54 °C and 55 °C, respectively, which indicates that the drug is completely dispersed into the polymer. The melting endotherm of Ilo was completely disappeared from complexes in the thermogram. This designates an improvement in the dissolution profile of Ilo from the complexes due to the amorphization of the drug.

FTIR Fourier transform infrared spectroscopy plays a vital role in interpreting the correlation between the functional groups of active molecules and excipients. In IR spectra, observed peaks depict characteristic functional groups which may lead to move or alter the intensity on contacting other molecules while the formation of complexes therefore demonstrates efficacious complexation [25]. The FTIR spectra of Ilo showed at 1262 cm^{-1} due to C-F stretch, 1352 cm^{-1} due to N–O stretch, 1668 cm^{-1} due to C=O stretch, and 2949 cm^{-1} due to C–H stretching vibration. Likewise, Kolliphor P-188 displayed 1100 cm^{-1} due to C–O stretching, 3502 cm^{-1} due to O–H stretching vibration, whereas 400–975 cm^{-1} belongs to O–H vibrations of characteristic peaks of carboxyl and alcohol group of tartaric acid. The FTIR spectra of complexes showed the disappearance of the drug characteristic peaks. The carbonyl group of Ilo has shifted from 1668 to 1669.90 cm^{-1} in TAPOL T indicating its involvement in the interactions. The intensity and shape of the characteristic peak had changed dramatically as compared with that of the pure drug indicating the bending and vibration movements of the drug due to the formation of the complexes (Fig. 2b) [8].

X-ray Diffraction (PXRD)

PXRD might be analyzed to check the physical state of drugs and complexes as revealed in Fig. 2c. The crystallinity of Ilo displayed multiple distinct peaks at $2\theta°$ values of 17.22°, 20.73°, 22.13°, 24.03°, and 39.77° [23]. Similarly, the diffractometer of tartaric acid was perceptibly exposed by sharp peaks at 25.54°, 29.54°, 30.25°, 36.36°, 37.16°, and 55.70°. Kolliphor P-188 has two distinctive peaks at 19.62° and 23.73° as shown in Fig. 2c. The diffractometer of TAPOL B depicts a diminution in the intensity of peaks of Ilo, predominantly at 17.22° and 39.77°, while TAPOL T exhibited total desertion of characteristic peaks of Ilo. Also, tartaric acid peaks have disappeared in the TAPOL T diffractometer. On

Table 1 Quality control tests of sublingual tablets

Characteristics	Results (mean ± SD)
Weight variation (mg; $n = 20$)	106.8 ± 3.98
Content uniformity (%; $n = 10$)	95.92 ± 1.6
Hardness (kg/cm^2; $n = 10$)	4.0 ± 0.0
Thickness (mm; $n = 20$)	2.2 ± 0.01
Diameter (mm; $n = 20$)	7.0 ± 0.01
Friability (%)	0.366
Disintegration time (s; $n = 6$)	9 ± 1

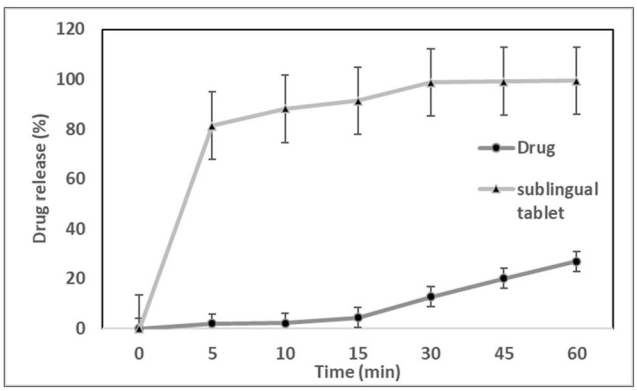

Fig. 4 Dissolution study of tablets ($n = 6$, mean ± SD)

another note, the characteristics of Kolliphor P-188 were present in both diffractometers of TAPOL B and T. These outcomes propose that the Ilo crystallinity was transformed to an amorphous form in TAPOL T. Hence, the addition of tartaric acid and the amorphous state of Ilo may contribute to improved solubility of Ilo by TAPOL T (Fig. 2c).

In vitro Analysis

The in vitro analysis was conducted to inspect the impression of enhanced solubility of Ilo from the complexes. The outcomes of the analysis were as shown in Fig. 2d. The analysis executed in phosphate buffer pH 6.8, barely 4.40 ± 0.01% of drug released within the first 15 min and 27.0 ± 0.02% release, was detected in the late of 60 min by the drug. At the end of 15 min, binary and ternary complexes showed three and four folds increase compared with drug alone, respectively. At the end of 60 min, 50.29 ± 0.07% and 63.68 ± 0.05% drug dissolved from TAPOL B and TAPOL T, respectively. Thus, the dissolution studies showed that there was an increase in the dissolution solubility of the ternary complexes as compared with the binary complexes which might be ascribed to the addition of an auxiliary agent that supplements the solubilization of Ilo. From the results, TAPOL T revealed improved and quick dissolution when compared with the TAPOL B and drug. Thus, the inclusion of an acidic auxiliary agent may amplify the dissolution profile of the drug [8] (Fig. 2d).

Microenvironmental Studies (MepH)

After the addition of TAPOL T, the drastic change in pH was observed in dissolution media pH 6.8 when compared with TAPOL B. The minimum difference was observed in dissolution media pH 1.2 in both the formulation. The pH-dependent solubility behavior of Ilo can be easily correlated with its weakly basic nature and pKa (7.69). Ilo is predominately in an unionized form in the alkaline pH, which roots very low solubility of the drug, whereas in ternary complexes, in the presence of an acidifying agent, its carboxyl and alcohol group get deprotonated leading to the formation of soluble compound [1, 2, 8]. A similar solubility enhancement has been reported by us for iloperidone by formulating complexes using hydroxypropyl-β- cyclodextrin and tartaric acid [8]. Thus, tartaric acid helps to create an acidic microenvironment around the drug, and thus, it may aid in drug release (Fig. 3) [22].

Quality Control Tests of Tablets

We formulated the tablet for the maximum dose of Ilo, i.e., 12 mg. Quality control results for Ilo sublingual tablets are tabulated in Table 1. Weight was found to be uniform across all the tablets. Based on the content uniformity results, the tablets had a uniform drug distribution [22]. Hardness replicates the physical strength of a tablet. Thickness and diameter offer an idea about the consistency of the tablets. These tablets showed uniform hardness, thickness, and diameter. The friability of the tablets was found less than 1% which proposes that the tablet can withstand abrasion in packaging, transporting, and handling [23]. Analysis of disintegration is of utmost importance while formulating a sublingual tablet, as it must disintegrate quickly when placed in the mouth. The tablets had a fast disintegration time which resulted in faster dissolution. As shown in Fig. 4, 81.36 ± 0.74% of the Ilo was released within 5 min when compared with the plain drug (1.97 ± 0.38%). The enhanced solubility and dissolution may improve bioavailability of Ilo when administered through the sublingual route. The bioavailability enhancement has been reported by us for Ilo by formulating sublingual films [5]. In the same loop, several researchers reported that sublingual formulations showed an increase in the bioavailability [26–28]. This outcome might be elucidated by numerous aspects, counting enhanced drug wetting and change in pH in the presence of the auxiliary agent, also the amorphous state of the Ilo in the sublingual tablet [8].

Conclusion

We formulated for the first time a sublingual tablet of iloperidone at a maximum dose of 12 mg. Thus, scale down can be possible which will be a key advantage of this formulation. The formulation depicts excellent uniformity, rapid disintegration. The present study demonstrates the increase in solubility and release of Iloperidone due to the microenvironmental pH effect from sublingual tablets. Hence, microenvironmental pH modification is a good approach to increase drug solubility for the management of schizophrenia.

Compliance with Ethical Standards

Competing Interest The authors declare that they have no conflict of interest.

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