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Original Article

DEVELOPMENT AND EVALUATION OF TASTE MASKED ORO-DISINTEGRATING TABLETS OF ITOPRIDE HCl USING DIFFERENT CO-PROCESSED EXCIPIENTS: PHARMACOKINETICS STUDY ON RABBITS

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ABSTRACT

Objective: This study aimed to mask the bitter taste of itopride HCl using the solid dispersion method by solvent evaporation technique and formulate an oral disintegrating tablet (ODT) by direct compression method using different co-processed excipients.

Methods: Nine formulae of solid dispersion were prepared to mask the bitter taste of Itopride HCl using Eudragit EPO® and mannitol at different ratios after compatibility studies using infrared spectroscopy (IR). The prepared formulae were subjected to different physicochemical characterization, *in vivo* taste evaluation, and drug content. The best-selected formulae were used to formulate 10 different ODTs. The prepared tablets were evaluated through hardness, drug content, *in vivo-in vitro* disintegration, IR, wetting time, and finally, dissolution studies. The selected formula was subjected to a pharmacokinetic study compared to the brand.

Results: F5, drug: Eudragit EPO® (1:2) and F8, Drug: Mannitol: Eudragit EPO® (1:1:2) formulae were selected as the best taste-masked formulae based on *in vivo* taste evaluation, which were used to formulate ten ODTs. The dissolution rate for the prepared ODTs was rapid if compared with the ordinary oral tablets. Statistical significance was obtained using one-way ANOVA among ODT formulae. The optimum tablet Prosolv SMCC 90® based formula (T10) had friability 0.15, wetting time 4±0.35 sec, *in vitro* dissolution 100.08±0.028% just after 2 min, where the *in vitro* disintegration time and *in vivo* disintegration time were 4±0.12 sec and 12±0.049 sec respectively. The relative bioavailability of ODT containing Prosolv SMCC 90®was increased significantly compared to the brand.

Conclusion: The obtained results successfully confirmed the potential of the promising Prosolv SMCC 90® based formula (T10) to produce rapid onset action and in-time drug release instead of ordinary tablets containing itopride HCl and that provide by-passing the excessive degradation of drug by first-pass metabolism increasing the oral bioavailability from 60% of marketed drug Ganaton® to 88% for the prepared ODT (T10).

Keywords: Itopride HCl, Solid dispersion, Solvent evaporation, Taste masking, *In vivo* evaluation, Prosolv SMCC 90®, Eudragit EPO®

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INTRODUCTION

Patients presenting with epigastric pain and burning, early satiation, and postprandial fullness without any structural, organic, or systematic pathology are labeled as having functional dyspepsia (FD), which is a common problem whole around the world and often impacts on quality of life and work productivity [1]. Functional dyspepsia could easily be overlooked as the symptoms overlap with gastro-oesophageal reflux disease and irritable bowel syndrome [2, 3]. The regurgitation of stomach contents and acid into the esophagus caused by the spontaneous and repetitive opening of the lower esophageal sphincter or its improper closure is known as gastro-oesophageal reflux (GERD), which is a chronic case that also impacts on quality of life and work productivity [4].

Itopride is a prokinetic on the upper and lower GIT which is mediated by its dual mechanism of action as D2 receptor antagonist and cholinesterase inhibitory action [5, 6]. Itopride can relieve the clinical symptoms and improve the quality of life and mental health status of patients with Irritable Bowel Syndrome (IBS), GERD and FD accompanied by abdominal distension, so it is worthy of clinical promotion [7].

The bitter taste of itopride HCl is considered a pre-formulation problem. Taste masking changes the nature of powder material and affects rheological characteristics, mechanical strength, and disintegration behavior which are mandatory for the preparation of a pharmaceutical product meeting the official specifications [8]. Itopride HCl is 60% bioavailable due to the first-pass effect [9]. It is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase [10]. Thus, we incorporated itopride HCl in ODTs.

Orally disintegrating tablets are solid dosage forms that disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue are formulated to improve the disintegrating and dissolution rates of a pharmaceutical product [11]. To achieve rapid disintegration rates and improve the drug bioavailability. This dosage form is chosen when the patient has difficulty in swallowing and is also suitable for use in geriatric and pediatric patients or for those who suffer from conditions such as dysphagia [12].

It is estimated that only around 20% of medicinal ingredients can be compressed directly into tablets. The remaining materials lack the flow, cohesion, and lubricating qualities required for tablet production by direct compression [13]. The preference for direct compression as a tableting method raised the demands on excipient functioning, particularly in terms of flowability and compressibility. Co-processed excipients, in which excipients are mixed by sub-particle level interaction, have shown to be an appealing approach for creating high functionality excipients for use in the formulation of ODTs [14].

The novelty of the study is based on the formulation of taste-masked Itopride Hydrochloride orally disintegrating tablets using cost-effective methods in which solid dispersion of the drug-using Eudragit PO®, Mannitol, and a mixture of both were used, then direct compression with many novel co-processed excipients to formulate the ODT resulting in enhanced drug-bioavailability. To the best of our knowledge, no one used the same polymers, co-processed excipients, or methods in the formulation of taste-masked Itopride Hydrochloride orally disintegrating tablets.

MATERIALS AND METHODS

Materials

Itopride HCl ($C_{20}H_{26}N_2O_4$-HCl) was a gift from Global Napi drug company Ltd (6th October city, Egypt). Mannitol, El-Nasr Pharmaceutical Chemicals Co., (Egypt). Eudragit EPO®, Evonik

industries, (Germany)., Pharmaburst®800, was provided by SPI pharmaceutical company (Wilmington, DE, USA)., Lactochem® Microfine (Lactose microfine), was obtained from (Borculo Domo, Netherlands)., Prosolv SMCC 90®, Prosolv SMCC 50®, and Prosolv EASYtab Nutra was obtained from JRS Pharmaceutical company GmbHand Co. KG., Ethanol 96%, El-Nasr Pharmaceutical Chemicals Co. (Egypt).

Methods

Compatibility studies of Itopride HCl with the formulated additives

To investigate any possible interactions between the drug and the investigated polymers Fourier transform infrared spectroscopy (FTIR) was used. Physical mixtures of Itopride HCl and the polymers in the ratio of 1:1 of the best formulae were prepared and subjected to FTIR analysis.

FTIR spectra for blends

The above-mentioned drug (D), polymer (P), and D/P combinations were carried out using IR Affinity-1, Shimadzu, Kyoto, Japan. The samples were prepared as KBr disks compressed under a pressure of 6 tones/cm^2. The wavenumber selected ranged between 500 and 4000 cm^{-1}.

Preparation of taste-masked Itopride HCl blend by solid dispersion technique using the solvent evaporation method

In the solvent evaporation method of solid dispersion preparation [15], drug (Itopride HCl) and polymers (mannitol or Eudragit EPO®) were dissolved in Ethyl alcohol in different Drug: Polymer ratios mentioned in table 1. Solutions were mixed with constant stirring and solvent was evaporated. Solid dispersion was obtained after complete evaporation of the solvent, pulverized, and stored in an airtight container for further use.

Table 1: Composition of taste-masked Itopride HCl blend prepared by solvent evaporation technique

No.	Drug: polymer ratio	Itopride HCl (mg)	Mannitol (mg)	Eudragit EPO®(mg)
F1	1: 1	50	50	-
F2	1: 2	50	100	-
F3	1: 3	50	150	-
F4	1: 1	50	-	50
F5	1: 2	50	-	100
F6	1: 3	50	-	150
F7	1:1:1	50	50	50
F8	1:1:2	50	50	100
F9	1:2:1	50	100	50

Physicochemical characterization of the Itopride HCl SD blends

Pre-compression evaluations

Before compression, the prepared solid dispersions were evaluated for their micromeritics. Various parameters like bulk density, tapped density, angle of repose, flowability, compressibility index, and Hausner ratio were determined according to the official methods [16].

Bulk density and tapped density

Determination of Bulk and Tapped Densities is a method to determine the bulk densities of powdered drugs under loose and tapped packing conditions, respectively. Loose packing is defined as the state obtained by pouring a powder sample into a vessel without any consolidation, and tapped packing is defined as the state obtained when the vessel containing the powder sample is to be repeatedly dropped at a specified distance at a constant drop rate until the apparent volume of sample in the vessel becomes almost constant.

The powder was introduced in a graduated 10 ml cylinder using a powder funnel to read the unsettled apparent volume V_0, using the mean plane method (semi-sum of the values corresponding to the highest and lowest points of powder); also final tapped volume V_f was evaluated. All tests were made in triplicates and results were collected [17].

Compressibility index and hausner ratio

Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed as described above. As such, they are measures of the powder's ability to settle and they permit an assessment of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particulate interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio [18]. Various parameters were calculated as follows:

$$\text{Bulk density} = \frac{M}{v_0}$$

$$\text{Tapped density} = \frac{M}{v_f}$$

$$\text{Compressibility Index} = \frac{100 * (v_0 - v_f)}{v_0}$$

$$\text{Hausner Ratio} = \frac{v_0}{v_f}$$

Where: m is the weight of the powder used, V_0 is the apparent volume and V_f is the tapped volume.

Angle of repose

The fixed cone height method is used to calculate the angle of repose for each powder. To summarize, a glass funnel with an internal stem diameter of 5 mm is positioned 1 cm above a glass slide. Allow particles to flow softly through the funnel until a cone forms and reaches the funnel orifice. The angle of the cone to the horizontal is then recorded. The test was performed in triplicate for each sample and the results are presented as mean value±standard deviation (SD)[5].

The angle of repose was calculated using the following equation:

$$\text{Tan } \emptyset = \frac{h}{r}$$

Where h is the height of the powder cone and r is the radius of the powder cone.

***In vivo* taste masking evaluation**

In vivo taste masking evaluations for pure APIs, polymers, and all formulations were carried out in compliance with the World Medical Association's Code of Ethics (Declaration of Helsinki); also, an ethical committee approved this study, Faculty of Pharmacy, Cairo University, approval no. PI 1607. Volunteers were informed of the study's aim, procedures, and risks. All volunteers provided written informed consent before undergoing any study procedure. Twelve healthy volunteers (age 18–25) of either gender were chosen (male = 6, female = 6). 100 mg of blends were kept in the mouth for 60 seconds before being spat out. Mineral water was utilized to wash each volunteer's mouth in between the examination of two samples. The bitterness intensity scale (fig. 1) was used to record the bitterness instantly, with 1, 2, 3, 4, and 5 indicating least unpleasant, less unpleasant, neutral, more unpleasant, and most unpleasant [19]. Results are presented as mean value±standard deviation (SD), n=3.

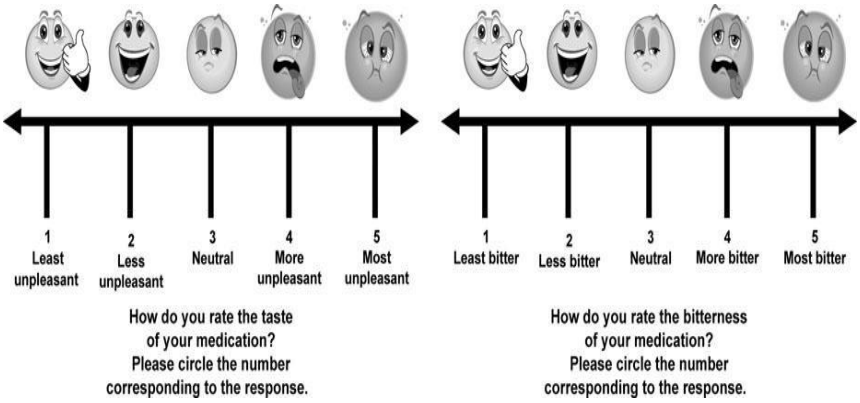

Fig. 1: Bitterness intensity scale

Drug content determination for blends

Ten-milligram sample of it pride HCl formulae was dissolved in a known volume of best solvent (distilled water: ethanol, 1:1) and the solution was filtered through using 0.45 µm membrane filter and itopride HCl was assayed UV spectrophotometrically at λ max 258 nm against a blank of the selected solvent [20]. Using UV-Vis spectrophotometer Shimadzu UV-1650 PC double beam–Japan, Then the drug content of different formulations was calculated. All results are presented as mean value±standard deviation (SD), n=3.

$$\text{Drug content}\% = \left(\frac{\text{Actual amount}}{\text{Theoretical amount}}\right) * 100$$

Preparation of ODTs by direct compression technique

Itopride HCl ODTs were prepared by the best taste-masked formulae (F5 and F8) with different co-processed excipients by direct compression technique, as shown in table 2. The powder was mixed using a V-shaped mixer (Erweka, Germany) then compressed into tablets using a single punch tableting machine (Royal Artist, India) of compression force 400 kg using a 7 mm flat punch and die set.

Table 2: Composition of taste-masked itopride HCl tablets prepared by direct compression technique amounts (mg/tablets)

Formulae	Selected formulae equivalent to 50 mg Itopride HCl		co-processed excipients (mg/tablet)				
	F5	F8	Pharmaburst®	Pro solve NUTRA C®	Lactochem Microfine®	Prosolve SMCC 50®	Pro solve SMCC 90®
T1	125	-	125	-	-	-	-
T2	125	-	-	125	-	-	-
T3	125	-	-	-	125	-	-
T4	125	-	-	-	-	125	-
T5	125	-	-	-	-	-	125
T6	-	150	150	-	-	-	-
T7	-	150	-	150	-	-	-
T8	-	150	-	-	150	-	-
T9	-	150	-	-	-	150	-
T10	-	150	-	-	-	-	150

Evaluation of prepared ODTs

Physicochemical and mechanical characterization of ODTs

Evaluation of ODTs was performed on the tablets of all formulae considering the visual inspection, weight, and content uniformity, thickness using a micrometer (BDM CO., Germany), hardness using tablet hardness tester (TH3/500, Copley scientific, UK), and friability using tablet friability tester (FR 1000, Copley scientific, UK) according to the pharmacopeial requirements (USP 39-NF 34).

Weight uniformity

Ten tablets from each formula were individually weighed and the mean of tablet weights was calculated [21]. Results are presented as mean value±standard deviation (SD), n=3.

Tablet friability

Ten tablets from each formula were precisely weighed and placed in the friability drum (Thermonik type, Campbell electronics, India). The tablets were rotated at 25 (rpm) for 4 min before being removed, dedusted, and properly re-weighed. The percentage weight loss was determined using the following equation and used as a measure of friability [22].

$$\text{friability }\% = \left(\frac{W1 - W2}{W1}\right) * 100$$

Where: w1= Initial weight of tablets or weight before a test

w2= Final weight of tablets or weight after the test

Tablet hardness

According to the British Pharmacopoeia, ten tablets from each formula were tested using a hardness tester (Thermonik type, Campbell electronics, India). The mean hardness was calculated in kg±SD, n=3.

Determination of the wetting time

A piece of circular tissue paper of 10 cm in diameter was placed in a Petri dish of 10 cm diameter. Ten milliliters of dye solution (methylene blue aqueous solution). A tablet was carefully placed on the paper's surface, and the time required for the dye solution to reach the upper surface of the tablet was noted as the wetting time (WT) [23].

***In vitro* disintegration time**

ODTs were placed in the baskets of the USP disintegration apparatus (Thermonik type, Campbell electronics, India). At 37±0.5 °C, the ODTs were added to 900 ml of distilled water. The disintegration time was defined as the time necessary for the tablet to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A digital stopwatch was used to

measure the disintegration time to the nearest second [24, 25]. All results are presented as mean value±SD, n=3.

Tablet drug content determination

Itopride HCl content of different formulated tablets was determined by dissolving one tablet of each formula in a known volume of the best solvent (distilled water: ethanol, 1:1), then the absorbance was measured spectrophotometrically at 258 nm (UV-Vis spectrophotometer, Shimadzu UV-1650 PC double beam–Japan) using the same solvent as the blank and the percentage drug content was calculated. Each experiment was carried out in triplicate, and the mean drug content in each formulation was determined [26].

***In vitro* dissolution test**

In vitro dissolution studies [27] were performed using (USP dissolution apparatus II tester (Heusenstamm, Germany), The dissolution test was performed using 900 ml of distilled water at 37±0.5 °C. The speed of rotation of the paddle was set at 50 rpm. oral disintegrating tablet of Itopride HCL (equivalent to 50 mg of Itopride HCL) was introduced in the dissolution medium. The dissolution tests were carried out for 2 h. Aliquots of 4 ml were collected after 2, 5, 10, 15, 30, 45, 60, 90, and 120 min and immediately replaced with the same volume of fresh medium. The samples were analyzed using a double beam UV-spectrophotometer and the absorbance was recorded at 258 nm. The *in vitro* dissolution studies were performed in triplicate and the results are presented as mean value±SD.

Compatibility studies of best prepared ODTs with the formulated additives

Fourier transform Infrared spectroscopy

FTIR spectra of the pure best-selected blend, best selected co-processed excipients, and physical mixture of both were recorded by IR Affinity-1, Shimadzu, Kyoto, Japan. The samples were prepared as KBr disks compressed under a pressure of 6 tones/cm^2. The wavenumber selected ranged between 500 and 4000 cm^{-1}.

Experimental design

The experimental results were analyzed using Design-Expert software version 13 (Stat-Ease, Inc., Minneapolis) table 3, to study the effect of variables on the ODTs' properties in terms of hardness, friability, disintegration time, wetting time, and dissolution. to reduce the number of experimental runs needed for conducting the study [28].

Table 3: The D-optimal design was used for the optimization of prepared ODTs

Factors (independent variables)	Factor type	Levels	
		Low	**High**
X_1: Co-process	Categoric	Absent	Present
X_2: Formulae	Categoric	F5	F8
Responses (dependent variables)		**Desirability constraints**	
Y_1: Wetting time		Minimize	
Y_2: Friability		Minimize	
Y_3: *In vitro* dissolution		Maximize	
Y_4: *In vitro* disintegration time		Minimize	
Y_5: *In vivo* disintegration time		Minimize	

***In vivo* studies**

Six New Zealand albino rabbits (obtained from animal house, Misr University for Science and Technology, MUST) weighing about 2-2.5 kg, with no previous diseases, in standard settings with commercially available food and cabbage, were included in the experiment. The protocol of this study was approved by the Research Ethics Committee in the Faculty of Pharmacy, Cairo University (PI 1607) Egypt, adhering to the "Guide for the Care and Use of Laboratory Animals" declared via the Institute of Laboratory Animal Research (Washington, DC, USA).

In our study, all rabbits were fasted for 12 h and given unlimited access to water. The treatment was initiated where all six rabbits were divided equally into two groups and given codes (A, B). Group A was given a commercial medicine (Ganaton®50 mg, Abbott, Egypt) that was administered orally to each animal. Whereas group B received the chosen ODT, by placing it in the rabbits' oral cavities using forceps until completely disintegrated.

At different time intervals (0, 5, 15, 30, and 45 min) following administration as well as 1, 1.5, 2, 3, 4, 5, and 6 h later., Blood samples were collected into heparinized tubes centrifuged at 4000 rpm for 15 min and the separated plasma was transferred into tubes and stored at-80 °c until assayed.

Pharmacokinetics analysis

The measured plasma Itopride HCl concentration was plotted against time and compared to the commercial formulation Ganaton®. The studies were carried out in accordance with the CPCSEA (Committee for the Prevention, Control, and Supervision of Experimental Animals) recommendations.

The peak plasma concentrations (C_{max}) of Itopride HCl and the time of its occurrence (T_{max}) were estimated using the concentration-time data. The area under the plasma concentration-time curve (AUC) from time zero to the latest time recorded (AUC_{0-t}) was calculated using the linear trapezoidal method [23].

Assay of Itopride HCl

Diethyl ether was used to extract itopride hydrochloride from serum matrix using a liquid-liquid extraction technique. A reverse phase C18 column (250 mm4.6 mm, 5 µm) with isocratic elution was used to achieve chromatographic separation. The mobile phase, acetonitrile, and 0.05M phosphate buffer were utilized at a flow rate of 1.0 ml/min, and the eluents were monitored at 258 nm [29].

RESULTS

Compatibility studies of Itopride HCl with the formulated additives

Interactions between drugs and excipients play a vital role concerning the physicochemical properties and performance of certain formulations. In this study, FTIR has been used to investigate possible physical and chemical interactions occurring between the drug and the polymers used [30].

Fig. 2 showed the IR spectrum of (a) pure Itopride HCl it was quite matching with [31]. FTIR spectrum of Itopride HCL showed characteristic peaks such as 1269.16 cm^{-1} for C-O-C asymmetrical ether stretching (alkyl stretching), 1028.06 cm^{-1} for C-O-C asymmetrical ether stretching (aryl ethers), 3280.92 cm^{-1} and 3226.91 cm^{-1} for NH stretching, 1629.85 cm^{-1} for NH bending, 1651.07 cm^{-1} for the C = O stretching, 1147.65 cm^{-1} for C-N stretching and 2943.37 cm^{-1} and 2966.52 cm^{-1} for C-H.

(b) and (c) showed the IR spectra of polymers were used (Eudragit EPO® and Mannitol, respectively). While (d), (e), and (f) showed the IR spectra for a possible physical mixture of Itopride HCl with polymers. It is noted that there is no absence of any characteristic peaks; this corroborates the absence of any physiochemical interaction(s) and incompatibility between the drug and polymers.

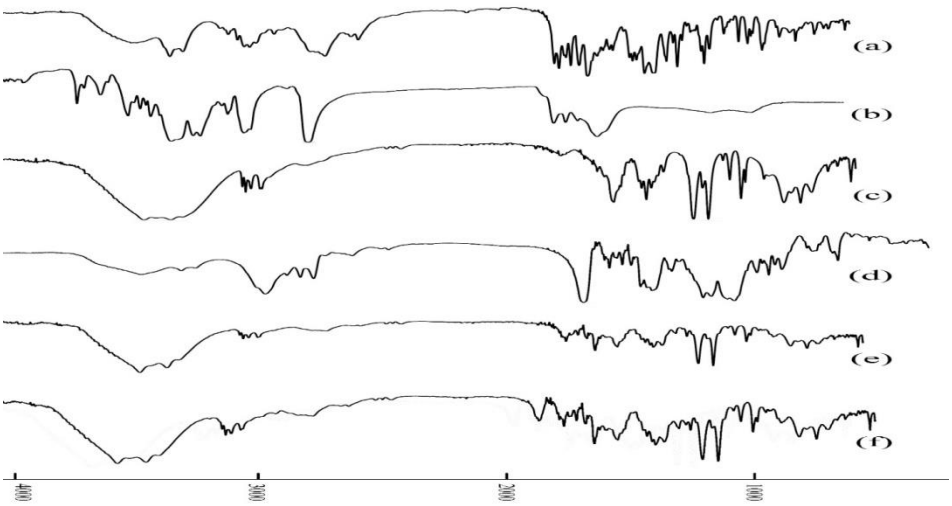

Fig. 2: FTIR spectrum for (a) Itopride HCl, (b) Eudragit EPO®, (c) Mannitol, (d) Itopride HCl+Eudragit EPO®, (e) Itopride HCL+Mannitol, (f) Itopride HCl+Eudragit EPO®+Mannitol

Physicochemical characterization of the Itopride HCl SD blends

Precompression evaluations

Solid dispersions were evaluated for bulk density, tapped density, angle of repose, compressibility index, and Hausner ratio. The results of powder flow properties (table 4) indicated good flow characteristics of all solid dispersions. It was noted that in the case of using Eudragit EPO®, solid dispersions showed very free-flowing properties as in F4, F5, and F6 while in the case of mannitol, solid dispersions showed free-flowing properties as in F1, F2, F3, F7, F8, and F9. this may be due to the difference between mannitol and Eudragit EPO® in particle size and energy [5, 32].

Table 4: Physical properties of solid dispersions of Itopride HCl

No.	Bulk Density (gm/ml) (mean±SD, n = 3)	Tapped Density (gm/ml) (mean±SD, n = 3)	Angle of Repose (mean±SD, n = 3)	Flowability	Comp. Index (mean±SD, n = 3)	Hausner ratio (mean±SD, n = 3)
F1	0.816±0.030	0.918±0.027	37.6±0.019	Free-flowing	11.11±0.04	1.125±0.019
F2	0.703±0.021	0.808±0.021	34.3±0.015	Free-flowing	13.04±0.015	1.15±0.020
F3	0.666±0.042	0.858±0.043	33.4±0.011	Free-flowing	20±0.012	1.25±0.032
F4	0.59±0.020	0.67±0.022	29±0.023	Very free-flowing	75±0.021	1.136±0.029
F5	0.686±0.011	0.755±0.015	29.7±0.025	Very free-flowing	44±0.023	1.1±0.021
F6	0.592±0.031	0.7105±0.029	29.98±0.013	Very free-flowing	96±0.021	1.2±0.034
F7	0.65±0.028	0.714±0.025	37.3±0.023	Free-flowing	6.667±0.023	1.07±0.029
F8	0.8±0.023	0.714±0.019	36.5±0.019	Free-flowing	10.714±0.012	1.12±0.021
F9	0.692±0.031	0.769±0.035	37.6±0.020	Free-flowing	10.345±0.026	1.115±0.017

***In vivo* taste masking evaluation**

It was noted that by using the solvent evaporation method, F5 (1:2) (Drug: EPO) and F8 (1:1:2) (Drug: Mannitol: EPO) were the best formulae for their evaluation to mask the bitter taste with a score = 1.16±0.4 and 1.33±0.51 respectively Least unpleasant (least bitter). While F6 (1:3) (Drug: EPO) was found to be the most bitter taste with a score =5.1±0.42 most unpleasant. The more bitter taste was ranked for (F1, F7, and F9) with a score =4.18±0.13 more unpleasant. The neutral taste score was ranked for (F2 and F4) with a score =3.02±0.08, while the less bitter score was ranked for (F3) with a score =2.11±0.17 less unpleasant.

Eudragit® EPO was chosen as the carrier for the taste-masked formula. It is a pH-dependent substance that is only soluble at pH levels lower than 5.5. By making use of this unique characteristic, we can prevent the bitter drug from being released from the formula in saliva (pH 6.2), disguising the bitterness caused by the drug in the oral cavity [33]. Moreover, the sweet taste of mannitol aids in masking the bitter taste of itopride HCl [6].

Drug content determination for blends

Estimation of drug content of the best taste-masked formulations indicated that the drug was uniformly distributed were F5 and F8 drug content % was 128.65±0.001 and 139.092±0.063 respectively, studies were performed in triplicate and results are presented as mean value±SD.

Physicochemical and mechanical characterization of ODTs

Table 5 shows that all the prepared tablets achieved the pharmaceutical specification for weight variation. The average thickness of prepared ODTs was from 2.92±0.04 mm to 4.01±0.04 mm. The reproducibility of the results confirmed the consistency of thickness and weights of all formulae. Furthermore, all ODTs did not break or show any capping, cracking, or chipping during the friability [34]. All ODTs showed an optimum range of hardness (from 2.8±0.26 kg to 3.40±0.36 kg) as it can provide enough strength and porosity and at the same time, ensure rapid wetting and disintegration of the tablets [35].

Weight uniformity

All formulations were within pharmacopeia specification for weight variation none of the tablets deviated from the average weight by more than 10% [36]. Where the weight of ODTs varied from (242.6 mg±0.07) to (251.1 mg±0.41) for F5 tablets and from (293.2 mg±0.63) to (301.3 mg±0.91) for F8 tablets.

Tablet friability

It was noticed that all ODTs, showed acceptable friability according to the British Pharmacopeia as it is ranged between (0.12% to 0.44%) [37]. The results showed that there is a significant difference among friability using different co-processed excipients. All results are represented by DX 13.

Table 5: Physical evaluation of the ODTs using different co-processed excipients

Tablet formulae	Weight (mg) (mean±SD, n = 3)	Hardness (kg) (mean±SD , n = 3)	Thickness (mm) (mean±SD, n = 3)	Friability (%) (mean±SD, n = 3)	Disintegration *in vitro* (sec) (mean±SD, n = 3)	Disintegration *in vivo* (sec) (mean±SD, n = 3)	Wetting time (sec) (mean±SD, n = 3)	Drug Content % (mean±SD, n = 3)
T1	242.8±0.84	3.01±0.11	3.04±0.05	0.13±0.003	13±0.10	22± 0.68	23±0.50	85.1±0.064
T2	249.1±0.35	3.005±0.30	3.02±0.06	0.28±0.01	9± 0.12	17± 0.35	32±0.50	95.07±0.042
T3	243.1±0.56	2.8±0.26	2.92±0.04	0.15±0.012	155± 0.12	21± 0.95	700±0.50	85.21±0.134
T4	242.6±0.07	3.02±0.56	2.97±0.05	0.43±0.003	6± 0.17	11± 0.50	6±0.51	92.25±0.028
T5	251.1±0.41	3.012±0.31	3.08±0.04	0.42±0.001	5±0.12	11±0.36	3±0.53	85.41±0.071
T6	296.4±0.35	3.02±0.40	3.85±0.09	0.44±0.015	6± 0.10	11±0.06	162±0.51	85.1±0.071
T7	293.2±0.63	3.014±0.74	3.9±0.05	0.25±0.002	5± 0.15	8±0.58	9±0.51	86.4±0.198
T8	298.5±0.77	3.40±0.36	3.64±0.05	0.12±0.001	190± 0.17	51±0.06	1426±0.53	86.31±0.071
T9	301.3±0.91	3.08±0.36	3.78±0.05	0.37±0.002	11±0.10	10±0.51	5±1.01	85.2±0.071
T10	296.7±0.07	3.017±0.25	4.01±0.04	0.15±0.01	4±0.12	12±0.049	4±0.35	85.01±0.064

Wetting time

For the WT, it was observed that the WT of ODTs ranged from (3±0.53 sec, T5) up to (1426±0.53 sec, T8). it was found that all prepared formulae had acceptable WT (<180 sec) [38] except T3 and T8. By comparing different types of co-processed excipients-based formulae with the mixture, data revealed that while Lactochem ODT-based formula (T3) and (T8) showed relatively longer WT than other formulae ($p<0.05$). These results were attributed to the presence of lactose in its structure and this result agrees with [39].

***In vitro* disintegration time**

Table 5 displays the *in vitro* DT results of all ODTs. According to the European Pharmacopeia, the limit for the DT of ODTs is 3 min [38]. As a result, all ODTs had acceptable DT values ranging from 4±0.12 s to 190±0.17s. The results revealed that Pro solve SMCC 90® (T10) had significantly ($p<0.05$) the fastest DT, while Lactochem Microfine ® (T8) had the longest DT when compared with other formulae which was in good correlation with WT results. Similar findings were reported in [40].

Drug content of tablets

For drug content, all formulae complied with the United States Pharmacopoeia (USP 39-NF 34) limits [41]. as shown in table 5.

***In vitro* dissolution study**

Fig. 3 and 4 display the *in vitro* dissolution profile of ITO HCl from the different ODTs. The amount of Itopride HCl dissolved after 2 min was taken as a parameter for comparison between the different ODTs. The results showed that Pro solve SMCC 50® based formulae (T4, T9), Prosolv SMCC 90® based formulae (T5, T10), and Pharmaburst® based formulae (T6) all of them showed a high percentage of drug dissolved after 2 min. Results were in accordance with those obtained from *in vitro* and *in vivo* DT and WT when compared with the other formulae. Results showed that the presence of Pro solve SMCC in formulae provides rapid dissolution profiles due to the silicified microcrystalline cellulose nature that forms the co-process [42]. While in the case of (T1) which was completely released after 15 min, the presence of Pharmaburst® improves Physicochemical and Mechanical Characterization of ODTs this could be explained by the higher capacity of crospovidone as a super disintegrant, as it had rapid capillary activity and pronounced hydration [43]. But in the case of (T6), however, the presence of Pharmaburst®; the physicochemical and mechanical characterization of ODTs didn't meet our satisfaction may be due to the presence of mannitol in (F8), which was the core for (T6) and then the amount of mannitol became more than the amount of sorbitol that is present also in Pharmaburst® structure and having favorable hydration capacity than mannitol due to the presence of equatorial OH on the C-2 atom resulting in more hydration and high wetting capacity is contrary to mannitol having an axial OH on C-2 atom [44]. Also, this increases the wetting time and DT; these results agree with Jacob *et al.* [45] who observed similar results and stated that MCC and mannitol exhibit non-wetting properties due to the formation of a central rigid core leading to delaying the disintegration. While in the case of Lactochem Microfine® based formulae (T3, T8) the presence of lactose may be the result for the delayed dissolution, as mentioned before. Finally, in the case of Pro solve NUTRA C® based formulae (T2, T7) it was observed delaying of drug release; this due to the presence of sodium stearyl fumarate (SSF), which is Fatty acid esters lubricant [46] had some negative effects on the *in vitro* dissolution of immediate-release tablets, same findings were reported in Baclofen-Meloxicam ODT [47].

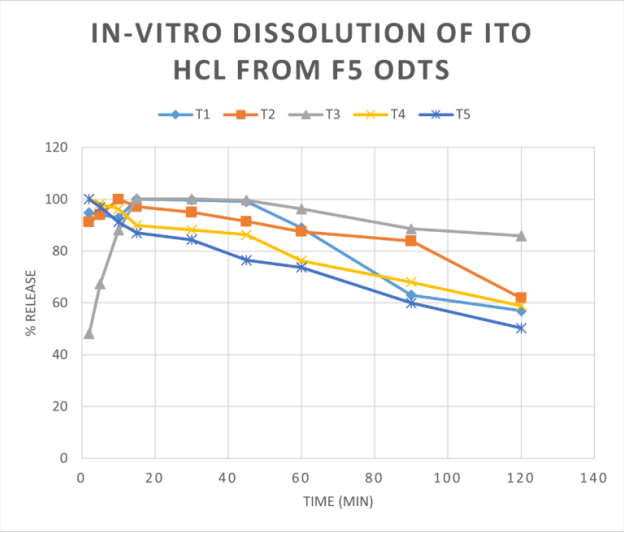

Fig. 3: *In vitro* dissolution profile of Itopride HCl from F5 prepared ODT (results are presented as mean value, n=3)
Abbreviations: ITO HCl: Itopride Hydrochloride

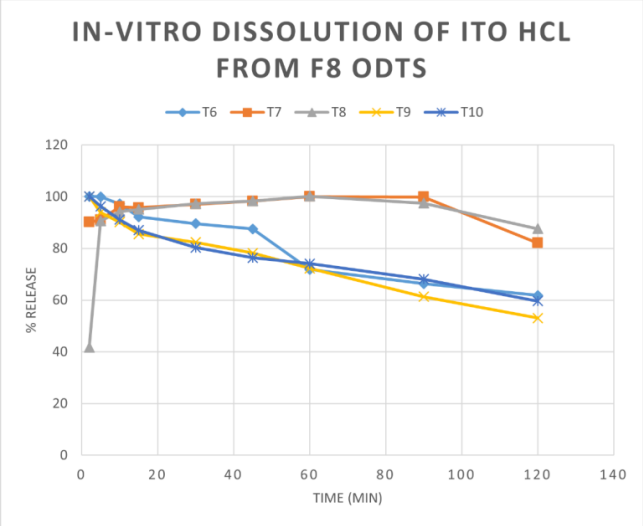

Fig. 4: *In vitro* dissolution profile of Itopride HCl from F8 prepared ODT (results are presented as mean value, n=3)

Table 6: Output data of the D-optimal design analysis of prepared ODTs (mean value±SD, n=3)

Response	Y_1: Wetting time	Y_2: Friability	Y_3: *In vitro* dissolution	Y_4: *In vitro* disintegration time	Y_5: *In vivo* disintegration time
Minimum (mean value±SD, n=3).	3.09±0.53	0.12±0.001	41.03±1.039	3.9±0.12	8.41±0.58
Maximum (mean value±SD, n=3).	1426±0.53	0.44±0.001	100.21±0.134	190.2±0.17	52.19±0.06
R-squared	1.0000	0.9904	0.9998	1.0000	0.9995
Adjusted R-squared	1.0000	0.9817	0.9997	1.0000	0.9990
Predicted R-squared	1.0000	0.9615	0.9993	1.0000	0.9979
Adequate precision	4986.242	25.050	209.756	1152.331	153.455

Table 7: Solutions for 10 combinations of categoric factor levels (mean value±SD, n=3)

Number	CO-process (X_1)	Formulae (X_2)	Wetting time (Y_1) (mean value±SD, n=3).	Friability (Y_2) (mean value±SD, n=3).	*In vitro* dissolution (Y_3) (mean value±SD, n=3)	*In vitro* disintegration (Y_4) (mean value±SD, n=3)	*In vivo* disintegration (Y_5) (mean value±SD, n=3)	Desirability	
1	PRO SOLVE SMCC 90	F8	4.335±0.35	0.15±0.01	100.08±0.028	3.96±0.12	11.805±0.51	0.964	Selected
2	PHARMABURST	F5	23.005±0.5	0.1305±0.003	94.8±0.42	13.155±0.1	22.3±0.68	0.891	
3	PRO SOLVE NUTRA C	F8	9.055±0.51	0.2625±0.002	90.11±0.09	5.005±0.15	8.755±0.58	0.853	
4	PRO SOLVE NUTRA C	F5	31.6±0.5	0.3±0.01	91.2±0.42	9.08±0.12	16.95±0.35	0.778	
5	PRO SOLVE SMCC 50	F8	4.98±1.01	0.378±0.002	100.095±0.77	11.055±0.1	10.08±0.51	0.709	
6	PRO SOLVE SMCC 90	F5	3.115±0.53	0.419±0.015	100.05±0.22	5.205±0.12	11.55±0.36	0.57	
7	PRO SOLVE SMCC 50	F5	6.09±0.51	0.4245±0.001	100.1±0.14	6.085±0.17	11.075±0.06	0.537	
8	PHARMABURST	F8	164.95±0.51	0.425±0.003	100.105±0.13	6.005±0.1	11.04±0.5	0.521	
9	LACTOCHEM REGULAR	F5	704.75±0.5	0.155±0.012	48.08±0.03	155.01±0.12	20.975±0.95	0.373	
10	LACTOCHEM REGULAR	F8	1424.5±0.53	0.121±0.001	41.765±1.04	189.75±0.17	51.64±0.06	0.011	

Experimental design

Adequate precision assures the ability of the model to navigate the design space when the measured signal to noise ratio is greater than 4, which was observed in all responses [48]. On the other hand, the predicted R^2 is a measure of the design's ability to predict values of different responses [49]. The predicted and adjusted R^2 values were in acceptable agreement table 6, ensuring there were no problems with the data or the model [28].

Desirability report produced from Design-Expert version 13 in table 7 showing that the best formulae selected based on different parameters (WT, friability, DT, and *in vitro* dissolution) was (T10), Pro solve SMCC 90® based formulae, which is taste masked by Eudragit EPO® and mannitol in ratio Drug: Mannitol: Eudragit EPO® (1:2:1). As also shown in fig. 5 and 6.

Compatibility studies for (F8) with the formulated additives in (T10)

Fourier transform infrared spectroscopy

Fig. 7 showed the IR spectrum of (g) F8, which is formed from solid dispersion of both Eudragit EPO® and mannitol with Itopride HCl, and as discussed before, there were no physical interactions between its components.

(h) showed the IR spectra of Pro solve MCC 90® that formed the best selected Itopride HCl ODT. While (i) showed the IR spectra for F8+Pro solve SMCC 90®. It is noted that there is no absence of any characteristic peaks; this corroborates the absence of any physiochemical interaction(s) and incompatibility between the drug and formulated additives.

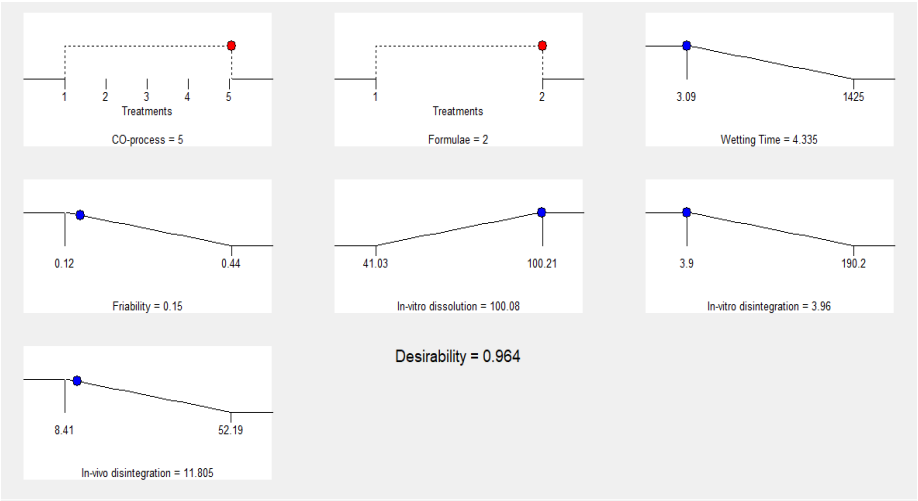

Fig. 5: Design expert desirability ramps for best-selected Formulae (T10)

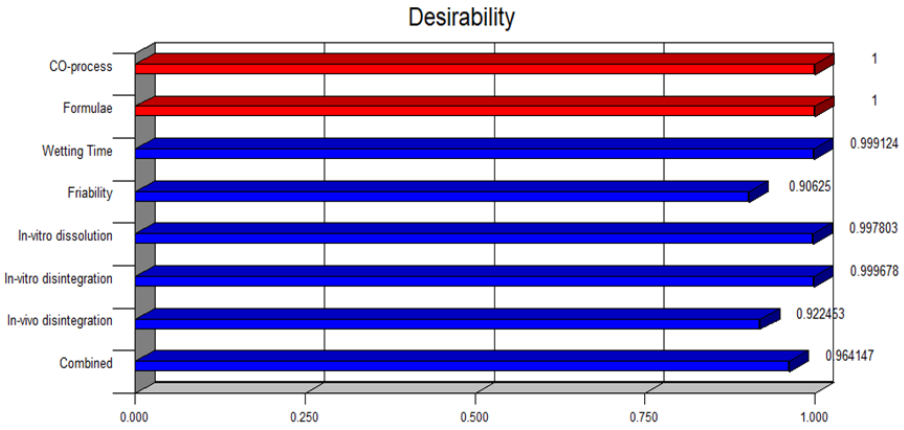

Fig. 6: Design expert desirability bar graph for best-selected formulae (T10)

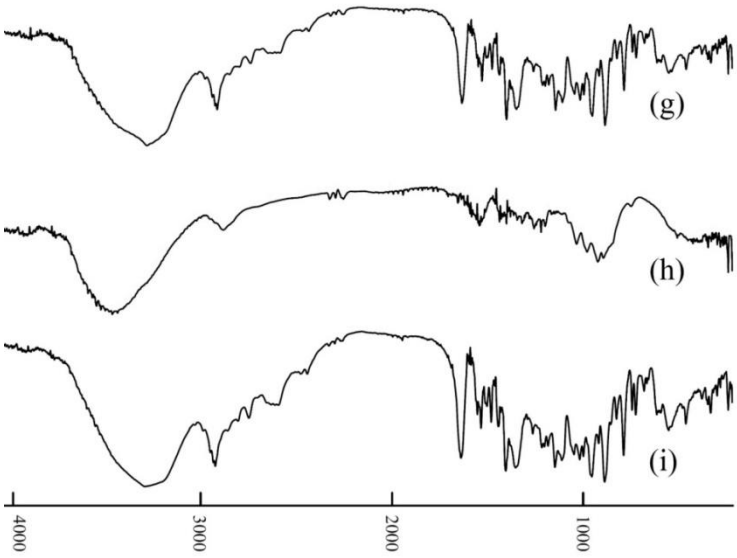

Fig. 7: FTIR spectrum for (g) F8, (h) Prosolve SMCC 90®, (i) F8+Prosolve SMCC 90®

***In vivo* study**

Fig. 9 showed the plasma concentration-time profiles of Itopride HCl ODT (group B) and the marketed oral tablet (group A). Rapid ascending of the Itopride HCl concentration after ODT administration compared to the oral marketed tablet in the shown curve indicated that the ODT form of the drug proceeds rapid action of the drug due to bypass first liver elimination and GIT degradation resulting in increasing the drug bioavailability with rapid reach to Itopride HCl maximum concentration.

The corresponding pharmacoeconomic parameters of Itopride HCl (C_{max}, T_{max}, and AUC $_{(0-6)}$ and relative bioavailability) in two different forms were listed in the table (8). The T_{max} of Itopride HCl was reduced to 60 min with increased C_{max} (288.789) from ODT compared to the T_{max} of 90 min with low C_{max} 270.8 for the marketed tablets. The rapid onset of action with great C_{max} value of the drug was achieved by application of the ODT form of our drug.

The systemic absorption of Itopride HCl from ODTs was greater than that of marketed tablets due to the presence of Prosovl SMCC 90®, which helped the drug to pass directly through the buccal cells. This could be approved by enhancing the value of AUC up to (41145.619) compared to the traditional form.

Based on the mentioned pharmacokinetics parameter, the calculated relative bioavailability of ODT (Prosovl SMCC 90®) enhanced up to 88% compared to the marketed form.

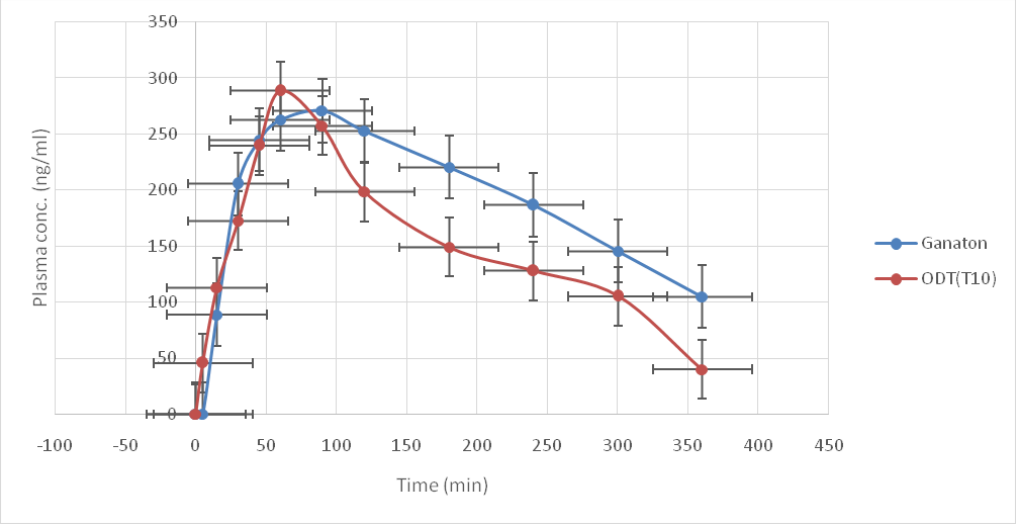

Fig. 8: Mean plasma concentration-time curve of Itopride HCl following the oral administration of the reference Ganaton® tablets group (A) and the selected ODT group B (results are presented as mean value±SD, n=3)

Table 8: Summary of the Pharmacokinetic Parameters of Itopride HCl Following the Administration of Commercial Oral Ganaton® Tablets and the (T10) ODT (mean value±SD, n=3)

Pharmacokinetic parameter (mean value±SD, n=3).	Ganaton®	ODT (T10)
C max (ng/ml)	270.802±1.487	288.789±1.11
T max (min)	90±0	60±0
AUC $_{(0-6)}$	36103.1729±374.19	41145.61972±563.27
Relative bioavailability	60%	87.74%

Abbreviations:
C_{max}: Maximum concentration (ng/ml)
T_{max}: Occurrence time of maximum concentration (minutes)
AUC $_{(0-6)}$: Area under the curve from zero time to 6 h

CONCLUSION

The bitter taste of Itopride HCl was successfully masked using Mannitol and Eudragit EPO® polymers by solvent evaporation technique. ODT (T10) was formulated using Taste masked formulae (F8) with Prosolv SMCC 90® by direct compression technique. T10 was the optimum tablet formula, which showed a superior dissolution profile, drug content, hardness, and disintegration time. Overall, the *in vitro* and *in vivo* results showed that the new prepared formula due to its rapid release easily provides effective and efficient tablets of Itopride HCl by the oral route as an ODT that provide by-passing the excessive degradation of drug by first-pass metabolism, increasing the oral bioavailability from 60% of marketed drug Ganaton® to 88% for the prepared ODT (T10).

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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