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Original Article

DEVELOPMENT AND CHARACTERIZATION OF ORODISPERSIBLE TABLETS OF PROPRANOLOL HYDROCHLORIDE USING CALCIUM CROSS-LINKED *CASSIA FISTULA* GUM AND CROSS CARMELLOSE SODIUM

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ABSTRACT

Objective: The present investigation was aimed towards developing calcium crosslinked derivative of carboxymethylated *cassia fistula* gum and crosscarmellose sodium based orodispersible tablets (ODTs) of propranolol hydrochloride for enhancing the bioavailability and efficacy.

Methods: Orodispersible tablets (ODTs) of propranolol hydrochloride was formulated using natural (a carboxymethylated derivative of *cassia fistula* gum) and synthetic polymer (crosscarmellose sodium) by wet and dry granulation, lyophilization and cotton candy methods and then finally compressed by direct compression. The prepared ODTs were evaluated for several parameters such as hardness, friability, *in vitro* disintegration time, *in vitro* drug release. *In vivo* and stability studies were carried out on optimized formulation coding PC1.

Results: Drug polymer interaction were judged by FT-IR, DSC and XRD. The optimized formulation coding PC1 prepared by cotton candy process containing 2.5% w/w of crosslinked *cassia fistula* gum has the least disintegration time (18.9±0.4s), weeting time (12.5±0.8s) and relased the drug of 88.2% within 10 min in contrast to croscarmellose sodium. *In vivo* absorption studies revealed that same formulation has C_{max} (µg/ml) 2.13±0.73, t_{max} (h) 0.21±0.17 and AUC_0^{∞} (µg ml^{-1} h^{-1}) 14.33±1.59.

Conclusion: This research manuscript clearly shows the successful development of the ODTs loaded with an antihypertensive drug, namely propranolol hydrochloride. The formulation developed by cotton candy process utilizing crosslinked *cassia fistula* gum as a natural superdisintegrant in contrast to other existing techniques can be a best option over synthetic superdisintegrant i.e. crosscarmellose sodium. The prepared ODTs was enhanced the absorption rate by lowering $t_{max,}$ which inturn enhance the bioavailability and the efficacy of drug.

Keywords: Hypertension, Croscarmellose sodium, Crosslinked *cassia fistula* gum, Lyophilization, Cotton candy method, Bioavailability

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INTRODUCTION

Oral route of drug administration is the most common, natural and obvious route to introduce the drug in the biological system. It is simple and convenient route offering maximum patient compliance and least medical supervision [1]. It is the best suited route for the drugs offering moderate to higher bioavailability and exhibiting varying pKavalues though the bioavailability varies a lot by this route [2]. The pH of the gastrointestinal tract (GIT) varies; hence the drugs with a range of pKa and solubilities are best suited to be administered by this route [3]. Also, this route offers an added advantage of the administration of huge doses, which is almost impossible with other routes. However, there are many challenges to have a predictable and dependable bioavailability and pharmacokinetic profile from this very route. The major factors constituting the challenging barriers and posing hurdles include, but not limited to the pH variability, intestinal mobility, gastric emptying time, hepatic and intestinal metabolism [4]. With an aim to design easily administrable drug products, newer tablets have been developed by pharmaceutical manufacturers, which can be simply placed and tongue and disintegrate/dissolve when come in contact with saliva. These systems eliminate the need of chewing and use of water for the ingestion of such oral products. Apart from numerous benefits, these oral tablets have been proved to be beneficial for paediatric, geriatric and psychiatric patients. As these systems can easily form solutions or dispersions within a fraction of min and the drug particles are exposed to the highly vascular oral cavity, there is substantial absorption of the drug, which is not feasible with the conventional oral dosing. Meanwhile, there are no choking hazards and miniscule chances of sticking and obstruction of the food passage, these systems are far safer than the other comparable oral/peroral products. Henceforth, ODTs are regarded as the systems which enhance the safety as well as efficacy of the drugs administered by this technique [5]. Propranolol hydrochloride is a β-adrenoreceptor antagonist, which inhibits the orthosympathetic pathways by competing with the catecholamines. It is use to control hypertension by targeting the peripheral sites of the non-adrenergic systems. This drug is also used for the treatment of tachyarrhythmia and coronary artery disease. Even though this drug is potent, there are certain side effects preventing its wide applications. They include excessive hepatic metabolism, low bioavailability of 25%. In order to overcome all these factors produced by the conventional tablets, it was planned to prepare calcium crosslinked *cassia fistula* gum (CCG) based orodispersible propranolol hydrochloride tablets along with its exploration through various evaluation parameters.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride and crosscarmellose sodium was kindly supplied by Tidal Laboratories Pvt. Ltd, Himachal Pradesh, India. Seeds of *cassia fistula* were procured from Sugatu Global, Uttarakhand, India. PEG 400 and Hydroxypropyl methylcellulose (HPMC) were purchased from M/s Sigma-Aldrich, Bangalore, India. M/s Central Drug House, New Delhi, India supplied lactose, gelatin, talc, buffer reagents, mannitol, magnesium stearate and polyvinyl pyrrolidine. The solvents and the column [Oyster BDS premium C18 (250 x 4.6, 5 µm; Batch No: 43/053)] employed for the HPLC were procured from M/s Merck Specialities Pvt. Ltd., Mumbai, India. In all the protocols where ever there is a need, double distilled water was employed. All chemical procured are used as such without any other purification.

Methods

Extraction of *cassia fistula* gum

Plants of *cassia fistula* is widely distributed in India except for Jammu and Kashmir, Himachal Pradesh, Maharashtra, Odisha and Uttar Pradesh. For the present study, seeds were procured from the

authentic source-Sugatu Global [voucher no. SG-2018/04/05 dated 05/04/2018], Uttarakhand, India. The botanical identity of the plant was confirmed by Dr. Deepak Kumar Associate Professor from ACPTE, Mastuana Sahib, Sangrur, Punjab with ref. no. ACPTE/PG/PA-990 dated 02/05/2019.

Seeds kernel powder of *cassia fistula* (20 g) were used for the extraction of the gum. The powder slurry was prepared by soaking the powder in 200 ml of cold distilled water. To this slurry, 800 ml of boiling distilled water was added, subsequently boiled for 20 min using a water bath assisted with continuous stirring. The boiling was stopped after the scheduled time period and the system was left undisturbed for overnight to facilitate the sedimentation of protein and fibres. The clear supernatant was harvested after centrifugation for 20 min at 5000 rpm. The precipitation of the polysaccharides was completed by pouring the supernatant in the twice volume of ethanol while stirring. The obtained precipitate was washed sequentially with ethanol, diethyl ether and petroleum ether followed by drying at 40-45 °C. The final product was sifted through sieve number 120 and desiccated till further use [6-8]. Analytical techniques like FT-IR and NMR were employed to characterize the gum.

Carboxymethylation of *cassia fistula* gum

The previously reported method by Goyal *et al.* was employed to derivatize *cassia fistula* gum to carboxymethylated *cassia fistula* gum (CCG) [9]. The extracted gum (5g) was suspended in 16 ml of 11.25 M NaOH solution, maintained at 1-4 °C. After complete dispersion, 7 ml of 7.93 M chloroacetic acid was added with stirring. The stirring was continued for 1 h at ambient temperature. After 1 h, the temperature was raised to 75 °C and the system was further stirred for 30 min. A solution of methanol and water in the volume ratio of 8:2 was prepared and neutralized by adding ethanoic acid. The reaction mixture was cooled and added into the methanolic solution to precipitate the CCG and the precipitates were collected on muslin cloth. The filtrate was washed thrice with the neutralized methanolic solution and the harvested solid was dried for 4 h at 50 °C and sifted across sieve number 80. The final product was vacuum desiccated till further use [7].

Preparation of calcium cross-linked CCG

The calcium cross-linked derivative of CCG was prepared by method reported by Rai *et al.* [7]. The CCG (2.5 g) was dispersed in 50 ml of deionized water to fetch 5% w/v dispersion. To this dispersion, 50 ml of 0.45 M calcium chloride was added dropwise assisted with constant stirring, followed by dropwise addition of 50 ml of isopropyl alcohol. The thick and gelatinous mass of the calcium cross-linked CCG was harvested and washed with deionized water to remove the unreacted CCG. The endpoint of the washings was determined by the disappearance of red colour of the filtrate when mixed with standard magnesium–EDTA complex solution containing Eriochrome black T indicator solution. The precipitates were freeze-dried and passed from sieve number 80 and desiccated till further use.

Development and optimization of orodispersible tablets

For the development of ODTs of propranolol hydrochloride three methods of preparation viz. lyophilization method, cotton candy process and disintegrant addition technique.

Lyophilization method

Formula was developed in such a way that each tablet contains 10 mg of propranolol hydrochloride each with different amounts of binder and disintegrants, as shown in table 1. A total of 8 formulations were developed where the percentages of the binder (gelatin) and the disintegrant (*cassia fistula* gum) were kept fixed and the amount of the diluent, i.e. mannitol, was varied.

Table 1: Composition of orodispersible propranolol hydrochloride tablets developed by lyophilization method

Materials	LP1	LP2	LP3	LP4	LP5	LP6	LP7	LP8
Propranolol hydrochloride (mg)	10	10	10	10	10	10	10	10
Mannitol (mg)	210	300	350	400	210	300	350	400
Gelatin (%)	1	1	1	1	1	1	1	1
Cross linked *cassia fistula* gum*CCG (%)	-	-	-	-	2.5	2.5	2.5	2.5
Croscarmellose sodium*CCS (%)	2.5	2.5	2.5	2.5	-	-	-	-

*CCG= cross linked *cassia fistula* gum *CCS= croscarmellose Sodium

Propranolol hydrochloride, crosslinked *cassia fistula* gum/croscarmellose sodium and mannitol were weighed accordingly and added to warm gelatin solution. The solution was blended vigorously to form stable suspension. Obtained suspension was filled into the blisters of diameter 13 mm by a syringe and was kept at-40 °C for 3 h. Blisters were transferred into a freeze dryer and was dried for 48 h at a temperature of-55 °C and pressure of 18 mTorr. No cryoprotectant was added additionally due to the presence of mannitol in the system itself [10, 11].

Cotton candy process

Two formulas for the tablets developed by the cotton candy process were used with only the variation of the superdisintegrants, *viz.* CCG and CCS both at the same strength. As already disclosed, the amount of propranolol hydrochloride per tablet was 10 mg for each of the tablet. The method reported by Battist *et al.* was employed for the development of the two formulations [12]. Firstly, a shear form matrix was prepared, which comprised of 82.25% sucrose, 15% sorbitol, 2.5% CCG/CCS and 0.25% Tween 60. All the ingredients were handed mixed and then mixed mechanically. The floss was prepared using a floss machine at approximately 3000 rpm. The floss was chopped and further used. The tablet mixture was prepared using 4.5% propranolol hydrochloride, 2.5% CCG/CCS, 0.3% aspartame, 2.5% orange flavour, 0.5% PEG 400 and q. s. floss. The ingredients were properly mixed and for each tablet, 225 mg of the mixture was weighed and introduced in the mould of approx. 0.25 inches. The ingredients were tamped at 80 psi pressure and cured at 40 °C and 85% RH for 15 min.

Disintegrant addition method

Formulation of propranolol hydrochloride orodispersible tablets by granulation methods is shown in table 2.

Table 2: Composition of the orodispersible tablets of propranolol hydrochloride prepared by disintegrant addition method

Materials	F1	F2	F3	F4	F5	F6
Propranolol hydrochloride (mg)	10	10	10	10	10	10
Cross linked *cassia fistula* gum (mg)	20	20	20	-	-	-
Croscarmellose sodium (mg)	-	-	-	20	20	20
Hydroxypropyl cellulose (mg)	-	-	2	-	-	2
Polyvinyl pyrrolidone (mg)	-	2	-	-	2	-
Starch (mg)	2	-	-	2	-	-
Microcrystalline cellulose (mg)	33.5	33.5	33.5	33.5	33.5	33.5
Lactose (mg)	28	28	28	28	28	28
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5

Preparation of tablets by wet granulation method

Granules as per the composition disclosed in table 2 were prepared by mixing the drug with starch paste which acts as binder. The wet mass was passed through # 10 and dried for 24 h at 60 °C followed by passing through 20 mesh sieves. Tablets are prepared by compression in the presence of super disintegrants. Known amounts of granules were weighed and mixed with cross-linked *cassia fistula* gum/croscarmellose sodium and other ingredients for 10-15 min using blender. To this mixture, lactose and magnesium stearate were added and compressed into tablets using tablet punching machine [13, 14].

Preparation of tablets by dry granulation method

All the excipients along with propranolol hydrochloride, were weighed in the required amount for each formulation and added into blender for proper mixing. The mixture was evaluated for various flow properties and was processed for compression. Slugging and deslugging were involved, followed by the lubricant addition in the compression of tablets using punching machine [15, 16].

Physical characterization of the blend

Various techniques were employed to prepare the granules for the tablet. The blend for the compression of tablets was prepared using wet and dry granulation technique and was characterized for angle of repose, bulk density, compressibility index, Hausner's ratio and tapped density [17-19].

Characterization of the prepared orodispersible tablets

The organoleptic parameters like colour, shape and texture were evaluated by the senses. Size of the individual tablets out of a sample of 20 tablets was measured using vernire caliper and it was expressed in mm [20]. For weight variation study of propranolol hydrochloride, 20 tablets were randomly selected and weighed individually and weighed collectively too. Individual weight and average weight of tablets were determined. Monsanto hardness tester was used to determine the hardness of the tablet [21]. For the friability testing of the prepared tablets, roche friabilator was used. Friability of 0-1% is considered as acceptable range [22]. To determine the wetting time, a piece of tissue paper was double folded and placed in a petri plate containing 10 ml of water. A tablet was placed on the paper and time required for the completing wetting was note down [23]. Morphology of the formulated tablets was determined using scanning electron microscopy. Cross sections of the tablet were made and employed for the morphological determination of the developed ODTs [24]. Disintegration time of the tablets was determined using the method established in the USP. The USP disintegration apparatus used for the determination of disintegration time of ODTs and conventional tablets was same [25]. USP dissolution apparatus Type-II (paddle) was used to determine the percent drug release profile of the tablets in sorenson's buffer (pH 6.8). Collected samples were analyzed using HPLC. Release kinetic models like zero order, first order, higuchi and korsmeyer pappas equations were used to know the pattern of release for the tablets [26, 27].

***In vivo* studies of the prepared orodispersible tablets**

Animals

Animals used in the present investigation were procured from AIIMS, New Delhi. All the animals (unisex wistar rats) involved in the study were housed under the standard conditions and were provided free access to pellet, food and water. All the animals were divided into groups with 2 animals each (age: 4-8 w; weight: 200-250g). The institutional animal ethical clearance (vide letter no. ASCB/IAEC/13/19/141) was obtained before conducting the studies. Group-I contained control animals; Group-II was administered with pure propranolol hydrochloride; group-III with ODTs prepared using calcium crosslinked c*assia fistula* gum using cotton method and Group-IV comprised with marketed propranolol hydrochloride tablets (betacap 10 mg).

Pharmacokinetic studies

All the animals were kept under overnight fasting before the experiment and food was provide post 2 h administration of the dosing. During the administration of tablets, animals were placed into animal body restraint device so that the head of the animal alone was exposed. Both the jaws of the mouth were separated with a wooden tongue pressor and tablets were placed in the mouth of the animals. The dose of propranolol hydrochloride was 6 mg/kg was employed [26, 27]. 2 ml of water was supplied as it helps in the disintegration of the tablet. Mouth of the animal was kept open for 1 min using gentle strain to allow complete disintegration and prevention of chewing. Blood samples (0.2 ml each) were collected from the retro-orbital plexus/tail vein of the pre-anesthetized animals at the regular time intervals (0, 0.25, 0.5, 1, 2, 4, 6 and 12 h) after the administration of the tablet. All the collected blood samples were centrifuged at 3000 rpm for 10 min for the extraction of plasma. Drug content was analyzed using the already devloped HPLC method [28]. The obtained data was fitted into one compartmental open body model by peroral route and various pharmacokinetic parameters were calculated using PK solver software.

Bio-distribution studies

After 24 h of drug administration, animals were sacrificed and various body organs like brain, kidney, liver, lungs, heart and spleen were collected to know the amount of drug distributed to each organ. Collected organs were washed in normal saline and perfused to remove the blood traces. Homogenates were prepared in the saline by using a homogenizer. Drug was extracted from the homogenates and analyzed using HPLC method [29, 30].

Antihypertensive activity

Intra-peritoneal injection of N-nitro-L-arginine methyl ester (L-NAME) at the dose of 185 µmol/kg was used twice daily to induce hypertension in the wistar rats for one week. The injection volume was kept as 1 ml per 100 g of the animal weight. The blood pressure of the animals was monitored daily and the animals with systolic blood pressure in the range of 160-190 mm of Hg after one week of the L-NAME administration were labelled as the hypertensive rats for the antihypertensive protocols [31, 32]. The selected hypertensive animals were divided into a total of 3 groups of 2 animals each (n=6), i.e. groups receiving plain propranolol hydrochloride, marketed product and the optimized ODT of the drug. One analogous control group was also maintained, animals of which received only distilled water. The other groups received the prescribed treatment at the equivalent dose of 6 mg/kg of propranolol hydrochloride. Subsequent to dose administration to study the antihypertensive effect the systolic blood pressure was measured at the time intervals of 0 min, 15 min, 30 min, 1 h and 2 h. The non-invasive tail-cuff method was employed to measure the systolic blood pressure of each animal at the predetermined time point using an experimental blood pressure system

Stability studies

In accordance to ICHQ1A (R2) guidelines, accelerated stability studies for the cotton candy ODT was performed at 40±2 °C and 75±5% RH for 06 mo [33]. The developed ODTs packed in blister packs were charged for the stability studies and the observations were made on the basis of the disintegration time, dissolution and drug assay over an interval of two month. The obtained values of % drug assay at the three observation points. i.e. 2 mo, 4 mo and 06 mo were reported as per the ICH guidelines.

RESULTS AND DISCUSSION

Characterization of pure and crosslinked *cassia fistula* gum by FT-IR and NMR

The FTIR spectra of the pure and crosslinked CCG gum have been shown in the fig. 1. The peaks observed in the region of 3500–3200 $cm^{-1}$are the characteristic absorption bands owing to the stretching hydroxyl groups, whereas the stretching in the range of 3000–2850 cm^{-1} were result of the aliphatic stretching and the ones observed in the range of 1650 cm^{-1} were resultant of-CH-O-strechings. These peaks are characteristic of natural gums [34]. On the other hand, at the wavenumbers of 1020 cm^{-1}, 1070 cm^{-1}, and 1155 cm^{-1} the C-OH strechings due to the presence of glucan and mannose structures were observesd. The peaks corresponding to the streching of N-H and C-N at 1541 $cm^{-1}$and 1080 cm^{-1}, which

were conspicuous in native gum, disappeared after crosslinking. In the FTIR spectrum of the crosslinked gum, a higher shifting in the wavenumber of the absorption band at 3446 $cm^{-1}$was observed. This peak represents the streching of-OH groups, which decreased substantially after cross-linking [35]. The appearance of two additional peaks at 1411 cm^{-1} and 1028 cm^{-1} ensured the presence of the carboxymethyl groups in the crosslinked gum, representing the respective strechings of C-O and C=O groups [36].

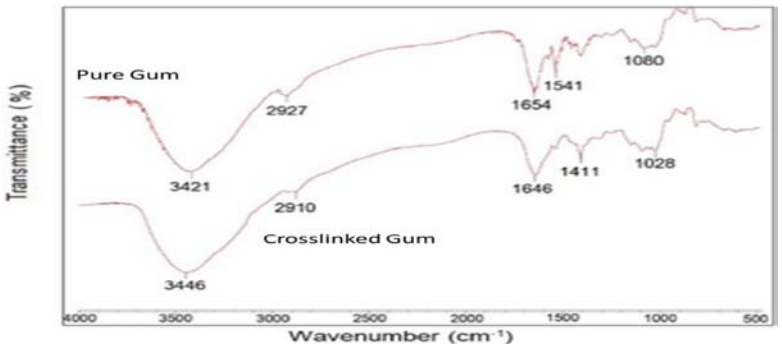

Fig. 1: FT-IR spectra of both the native gum and the crosslinked gum

The proton-NMR data have been represented in fig. 2 and fig. 3. Many researchers employ NMR as a tool to characterize natural polymers, but even the international union of pure and applied chemistry (IUPAC) is also of the opinion that the NMR is a relatively less sensitive tool to characterize the complex materials like natural polymers [37]. The proton NMR of the native gums shows the peaks-OH at 3.5 and 1-2 ppm, whereas the-OH peaks reflected at 3.5 ppm were absent in the NMR of the crosslinked polymer indicating the succesful reaction. Also the peaks between 1.531-1.558 ppm indicated the presence of numerous protons of methyl groups in the cross-linked polymer vouching the succesful crosslinking [38].

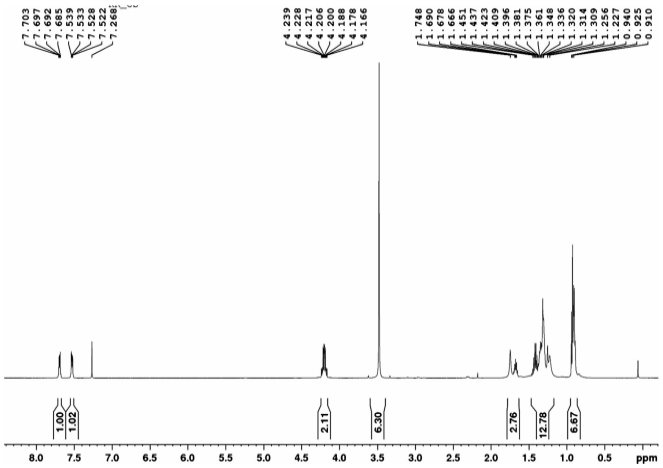

Fig. 2: ^{1}H-NMR of native *cassia fistula* gum

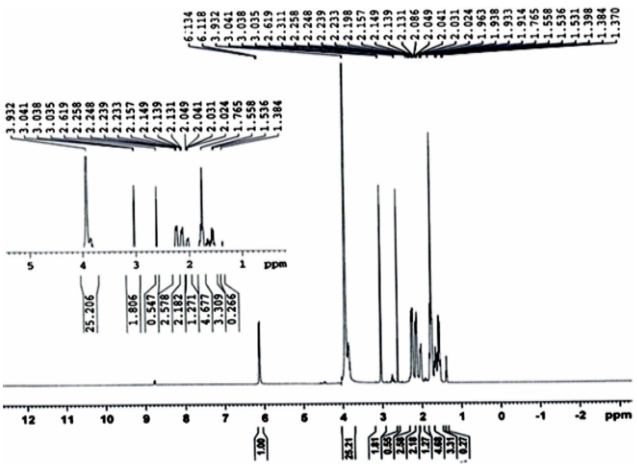

Fig. 3: ^{1}H-NMR of cross linked CCG

X-Ray diffraction

The XRD pattern of pure propranolol hydrochloride, the excipients and the physical mixture have been shown in fig. 4. The pure drug as represented by fig. 4(a) is absolutely crystalline in nature, whereas the excipients were observed to be relatively amorphous. The physical mixture was also observed to be more of amorphous nature.

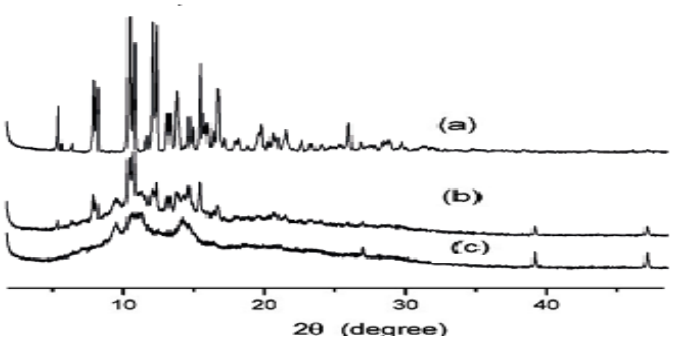

Fig. 4: Powder X-ray diffraction pattern of (a) pure propranolol hydrochloride (b) The excipients (c) The physical mixture

Differential scanning calorimetry

In the DSC thermogram of propranolol hydrochloride a sharp endothermic peak at 167.56 °C represented its phase transition, i.e. melting point. The excipients were found to be compatible with the drug as the melting point range of the drug remained same as depicted in fig. 5.

Flow properties of the blends

For the wet and dry granulation, process blends were prepared and were analyzed for flow properties. Blend of both wet and dry granulation was shown in table 2. Both cotton candy and lyophilization methods does not require any flowability henceforth, these parameters were not evaluated. Evaluated flow parameters of the powder blend were reported in table 3 [39].

Compatibility studies

As shown in fig. 6, there is neither appearance of any new peak nor the disappearance of the older peak in the FT-IR spectrum. Henceforth, it was concluded that there were no any compatibility issues of the drug with the selected excipients of the final ODT.

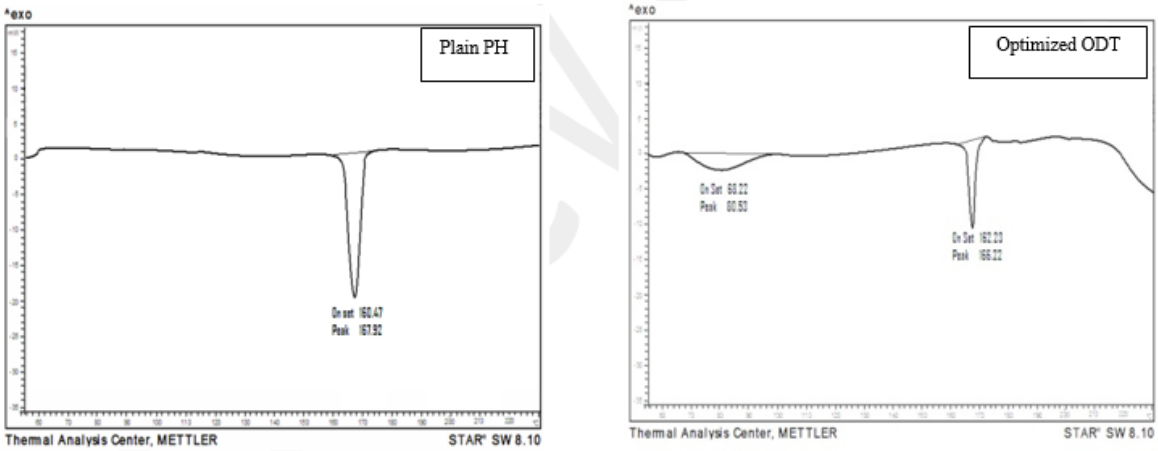

Fig. 5: DSC thermogram of the plain propranolol hydrochloride, excipients and physical mixture of the excipient and the drug

Table 3: Flow properties of various powder blends used for the development of tablets by wet/dry granulation technique

Wet granulation technique					
Formulation code	**Angle of repose (°)**	**Bulk density (g/cm³)**	**Tapped density (g/cm³)**	**Carr's index (%)**	**Hausner's ratio**
PW1	23.24±0.32	0.49±0.037	0.54±0.041	9.3±0.61	1.12±0.07
PW2	22.16±0.37	0.54±0.021	0.63±0.038	14.5±0.57	1.17±0.06
PW3	24.03±0.41	0.37±0.026	0.44±0.027	15.1±0.39	1.19±0.04
PW4	23.71±0.29	0.42±0.031	0.44±0.031	4.6±0.48	1.07±0.09
PW5	22.98±0.30	0.48±0.042	0.53±0.033	9.5±0.51	1.11±0.05
PW6	22.67±0.27	0.51±0.039	0.54±0.040	5.6±0.41	1.07±0.04
Dry granulation technique					
PD1	22.91±0.37	0.47±0.068	0.52±0.029	9.7±0.37	1.12±0.01
PD2	22.47±0.26	0.52±0.043	0.56±0.031	7.2±0.49	1.09±0.09
PD3	24.31±0.49	0.41±0.072	0.46±0.044	10.9±0.51	1.13±0.05
PD4	23.76±0.51	0.47±0.052	0.50±0.047	6.3±0.29	1.08±0.04
PD5	21.83±0.44	0.56±0.049	0.65±0.051	13.9±0.31	1.17±0.03
PD6	24.32±0.36	0.39±0.052	0.40±0.032	2.5±0.40	1.04±0.06

mean±SD, n=3 SD=standard deviation

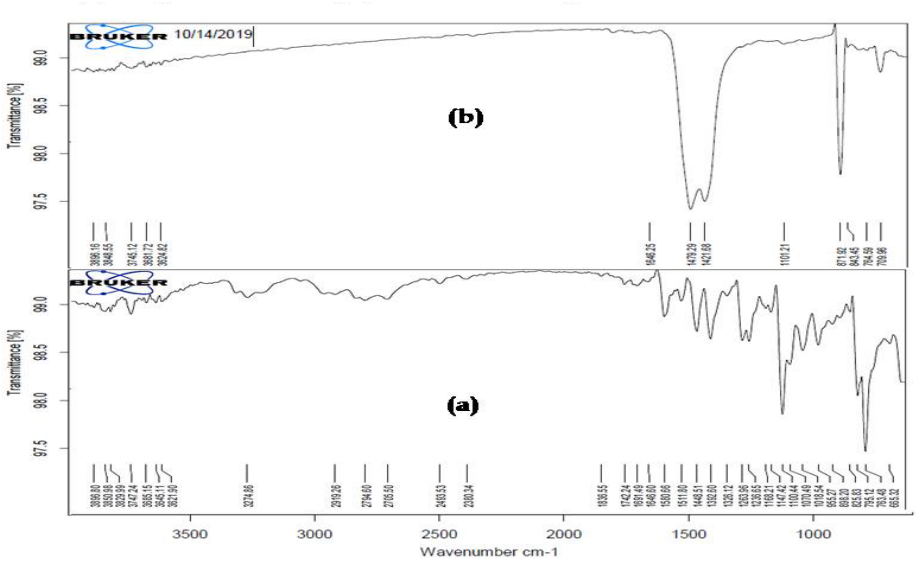

Fig. 6: FTIR (a) Propranolol hydrochloride (b) Mixture with the excipients

Characterization of the developed tablets

Physical evaluation of the tablets developed by wet/dry granulation

Thickness, diameter, hardness, weight variation and % friability of the developed tablets through dry and wet granulation techniques were shown in table 4.

Physical evaluation of ODTs developed by lyophilization and cotton candy process

Diameter, thickness, hardness, % friability and weight variation of tablets from all the lots of lyophilization method and cotton candy method were analysed and reported in table 5.

Evaluation of the developed propranolol hydrochloride loaded ODTs

Wetting time and disintegration time of the developed ODTs employing various methods were displayed in table 6. On the basis of the result obtained by lyophilization,dry granulation,wet granulation and cotton candy process formulations coded as PL8, PD2, PW2 and PC1 respectively were selected for further exploration. These results suggested that progress in drug release [13, 14]. From content uniformity assay it was found that all, the developed systems were showing the results in the prescribed limit. The assay of drug content showed that all the products contain more than 98.2% of drug. Based on the wetting and disintegration time of the all the developed lots, best four promising formulations were selected for further studies. PD2 and PW2 formulations of dry and wet granulation method, PL8 of lyophilization method and PC1 of cotton candy method was selected. Drug release profile of all these four formulations was observed and further one promising formulation which showed better release was used for *in vivo* pharmacokinetic evaluation. All four selected formulations have been highlighted in the tablet 6**.**

***In vitro* drug release studies**

Drug release profile of propranolol hydrochloride ODTs coding PC1, PL8, PW2 and PD2 was shown in fig. 7. The drug release profile ranged from 59.9% to 88.2% in 10 min after adding the tablets to the dissolution media i. e Sorenson buffer pH 6.8 which is similar to the saliva. From the study, it was found that cotton candy method resulted in the formulation which can yield a high amount of drug release which may be ascribed due to the high amount of sugars. Next to this method, product obtained through lyophilization method showed better results, which were due to high amounts of mannitol used in the formulation process. The drug release pattern was shown as PC1>PL8>PW2>PD2.

Formation of hydrotropic dispersion and the molecular dispersion within the tablet matrix helped in achieving the desired drug release pattern.

Table 4: Evaluation of developed tablets by wet/dry granulation technique

Wet granulation technique					
Formulation code	**Thickness (mm)±SD**	**Hardness (kg/cm²)**	**Weight variation (mg)**	**% Friability**	**%Drug content**
PW1	2.3±0.04	2.5±0.1	100±0.29	0.49±0.08	97.2±0.23
PW2	2.4±0.02	2.3±0.2	99±0.42	0.56±0.13	98.4±0.25
PW3	2.1±0.01	2.4±0.1	100±0.17	0.62±0.06	96.9±0.32
PW4	2.4±0.03	2.4±0.1	101±0.31	0.39±0.08	100.2±0.32
PW5	2.3±0.02	2.3±0.2	99±0.50	0.41±0.10	100.8±0.23
PW6	2.2±0.04	2.2±0.1	100±0. 34	0.52±0.08	99.2±0.31
Dry granulation technique					
PD1	2.4±0.03	2.3±0.1	99±0.32	0.51±0.11	97.7±0.59
PD2	2.5±0.04	2.2±0.1	100±0.46	0.47±0.11	97.2±0.34
PD3	2.3±0.02	2.2±0.1	101±0.33	0.55±0.10	99.4±0.35
PD4	2.0±0.04	2.3±0.1	99±0.49	0.37±0.15	98.3±0.39
PD5	2.3±0.05	2.4±0.2	100±0.21	0.41±0.09	98.9±0.24
PD6	2.2±0.03	2.2±0.1	100±0.35	0.62±0.13	97.5±0.21

mean±SD, n=3

Table 5: Evaluation of developed tablets by lyophilization and cotton candy method

Lyophilization method					
Formulation code	**Thickness (mm)±SD**	**Hardness (kg/cm²)**	**Weight variation (mg)**	**% Friability**	**%Drug content**
PL1	4.4±0.06	2.4±0.2	230±1.43	0.51±0.09	98.2±0.25
PL2	4.8±0.04	2.3±0.2	319±2.18	0.55±0.13	97.4±0.23
PL3	5.2±0.03	2.2±0.4	369±2.59	0.68±0.07	96.9±0.35
PL4	5.4±0.07	2.3±0.5	421±3.34	0.43±0.08	99.3±0.32
PL5	4.3±0.05	2.6±0.2	229±2.07	0.44±0.10	100.8±0.31
PL6	4.9±0.03	2.4±0.1	320±3.12	0.54±0.09	99.6±0.29
PL7	5.3±0.07	2.3±0.6	379±4.77	0.64±0.08	98.8±0.32
PL8	5.5±0.05	2.4±0.5	418±4.91	0.65±0.09	97.2±0.41
Cotton candy method					
PC1	4.2±0.05	2.2±0.1	224±2.6	0.34±0.06	99.8±0.43
PC2	4.1±0.03	2.3±0.1	225±2.3	0.37±0.09	98.6±0.36

mean±SD, n=3

Table 6: Wetting time and disintegration time of various formulations prepared by different methods

Lyophilization method		
Code	**Wetting time (s)**	**Disintegrating time (s)**
PL1	19.2±1.1	31.9±2.1
PL2	24.1±1.6	29.2±1.9
PL3	20.9±1.3	26.9±1.6
PL4	25.6±1.3	31.6±2.2
PL5	18.7±1.3	24.7±1.4
PL6	21.4±0.8	27.4±1.6
PL7	26.7±1.7	32.5±2.1
PL8	**14.4±0.6**	**19.2±0.7**
Dry granulation technique		
PD1	14.2±0.7	21.3±1.2
PD2	**15.7±1.0**	**22.8±0.8**
PD3	19.6±1.2	26.5±1.3
PD4	21.4±0.9	28.4±1.9
PD5	20.5±1.1	27.9±1.7
PD6	24.3±1.2	31.2±2.4
Wet granulation technique		
PW1	21.4±1.3	27.6±1.1
PW2	**14.6±1.1**	**21.5±1.0**
PW3	17.3±1.2	27.1±1.8
PW4	22.8±1.0	29.8±1.9
PW5	23.4±1.2	31.6±2.0
PW6	28.3±2.1	35.1±2.4
Cotton candy method		
PC1	**12.5±0.8**	**18.9±0.4**
PC2	23.2±2.6	39.6±2.9

mean±SD, n=3

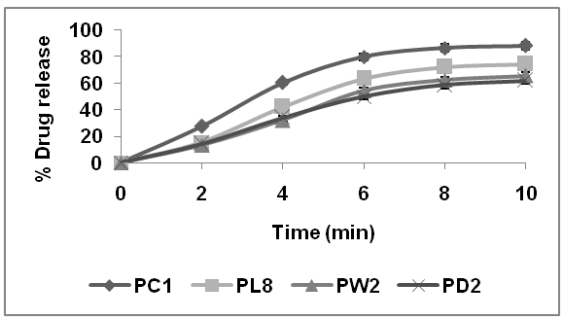

Fig. 7: Drug release profile of propranolol hydrochloride ODT code PC1, code PL8, code PW2 and code PD2, [mean±SD, n=3]

The data of the drug release from the formulation was fitted in zero order, first order, higuchi and korsmeyer peppas models to find the best fitted one by using the values of the coefficient of determination (r^2). The obtained values confirm that the developed systems offerd korsmeyer's-peppas drug release profile. This model represents that the drug release from the tablets was due to the erosion of the polymer layer (sugars in this formulations) along with matrix swelling resulting in the drug dissolution.

Scanning electron microscopy

Fig. 8 (a) and fig. 8 (b) show the SEM images of the pre-compressed and post-compressed powder for the propranolol hydrochloride ODT. As it is conspicuous that the powder material was segregated prior to processing, which has come closer after the formulation leading to the formation of a single unit dose.

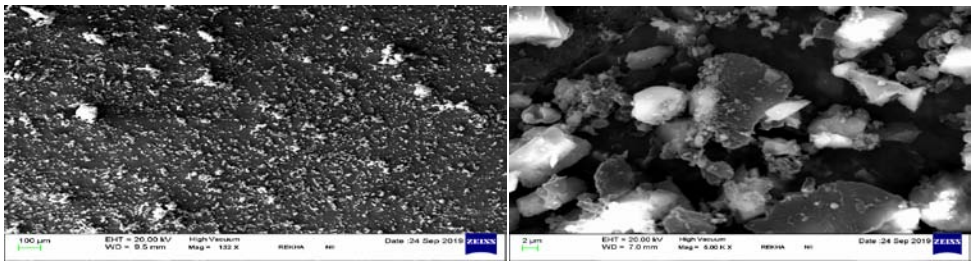

Fig. 8 (a): SEM of the pre-mix for the propranolol hydrochloride ODT Fig. 8 (b): SEM image of the final propranolol hydrochloride ODT

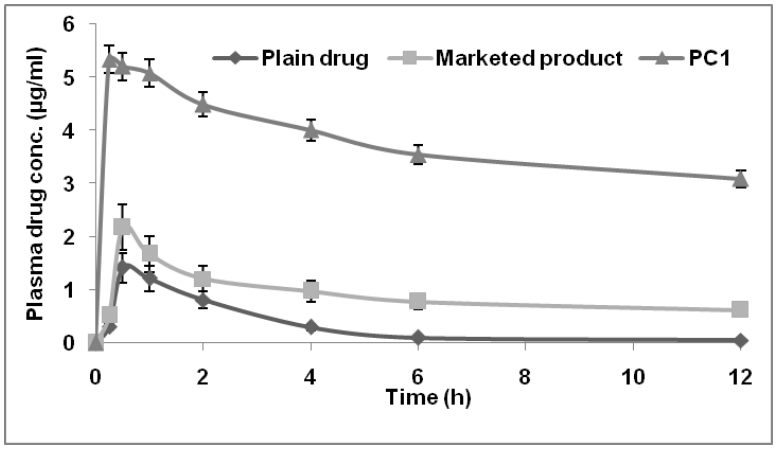

Fig. 9: The graph between plasma concentrations of propranolol hydrochloride in the rats receiving various treatments as a function of time, [mean±SD, n=3]

Pharmacokinetic studies

Fig. 9 portray the pharmacokinetic profile of the propranolol hydrochloride through the PC1 formulation of the cotton candy process which was selected from the drug release results.

From the graph, it was clear that the concentration of propranolol hydrochloride was high at every point in the plasma sample collected from the animals treated with the formulation prepared by cotton candy technique rather than the plain drug and marketed product. There was a significant difference in the concentration profile of both groups ($p<0.05$). This difference supports the advantage of developing a formulation and site of absorption of drug in the GIT.

***In vivo* absorption studies**

Obtained pharmacokinetic parameters were fitted in one CBM per oral model. From the results, it was found that the rate of elimination (K) was decreased by 4.25 times with the increase in plasma maximum concentration (C_{max}) resulted in the enhanced residence time of the drug within the biological system. Residence time of the drug in the body is represented by mean residence time (MRT), which was increased after the development of ODTs vis-à-vis plain drug. It was vivid from the area under the plasma concentration-time curve (AUC) that there was increase in bioavailability of the drug by almost 2.4 folds after the manufacturing process. These results proved that the development of ODTs helped in reducing the hepatic metabolism of the drug caused due to CYP3A4 enzyme. This may be due to the skipping of the hepatic portal system by the ODTs during the process of the drug absorption resulting in enhanced bioavailability.

Biodistribution studies

Fig. 10 displays the bar diagram showing the amount of drug present in each organ. This is a single point biodistribution study.

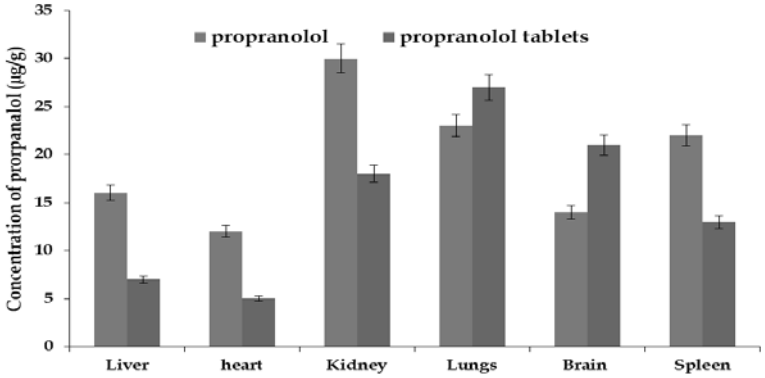

Fig. 10: The concentration of propranolol hydrochloride per gram of the organ mentioned after 24 h of dose administration, [mean±SD, n=3]

From the bar diagram shown in fig. 10, it was observed that the change in the amount of drug in animal groups was similar other than lungs and brain. The amount of drug in the liver and spleen is reduced in the animals treated with ODTs vis-à-vis plain drug ($p<0.05$). This result supports the pharmacokinetic profile of the ODTs as the drug availability is minimal at the site with microsomal enzymes. This indicates that the ODTs developed were absorbed through the buccal cavity, which helps to overcome the hepatic metabolism. This leads to an increase in the plasma concentration of the drug, which directly affects the pharmacological profile of the developed ODTs. These *in vivo* studies helped in the effective delivery of propranolol hydrochloride by developing the ODTs.

Antihypertensive activity

The results obtained from the antihypertensive pharmacological studies measuring the systolic pressure of the rats at various time points has been shown in fig. 11. The normal systolic pressure of the rats is 118.5±2.09 mm of Hg. However, the average systolic pressure in the disease control i.e. the hypertensive rat group not receiving any treatment, was observed to be around 180 mm of Hg vouching for the successful induction of the diseased state. From the observed data, it can be easily inferred that the reduction in the blood pressure was more pronounced in the group receiving optimized ODT (PC1) product *vis-à-vis* marketed product as well plain drug at

p<0.05. In a shorter duration of 15 min, the animals receiving the propranolol hydrochloride-loaded ODT exhibited a substantial reduction in the systemic blood pressure whereas the equivalent effect was observed in the marketed product receiving animal group at 60 min. The data unequivocally established the superiority of the developed system over the marketed product as well as the plain drug. The enhanced pharmacodynamic response of the developed system can be ascribed to the faster rates of absorption and slower elimination coupled with lower T_{max} and elevated C_{max} as inferred from the pharmacokinetic studies.

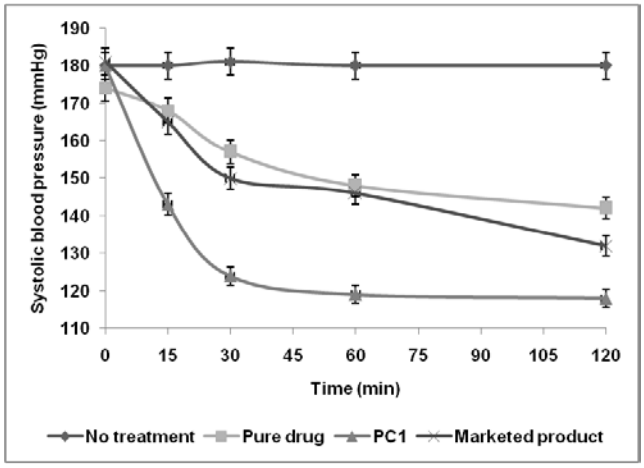

Fig. 11: Graph showing the pattern of systolic blood pressure in the various treatment groups [mean±SD, n=3]

Stability studies

The selected cotton candy based propranolol hydrochloride loaded ODT offered the best physicochemical and the biological outcomes in the real time scenario. Over the 6 mo accelerated stability assessment it was observed that no variation in the physical appearance and other studied parameters was observed, as shown in table 12.

Table 12: Accelerated stability data of the optimized ODT product (PC1) over a period of six months

Parameters	D							
	0	**30**	**45**	**60**	**90**	**120**	**150**	**180**
Physical appearance	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change
Weight	224 ± 2.6	224.3 ± 1.26	223.3 ± 1.48	223.6 ± 2.26	223.9 ± 1.49	224.6 ± 1.45	224.9 ± 2.38	224.3 ± 1.37
Hardness	2.2±0.1	2.2±0.4	2.1±0.2	2.1±0.7	2.1±0.5	2.1±0.3	2.0±0.4	2.0±0.2
Friability	0.34±0.06	0.34±0.09	0.35±0.03	0.35±0.05	0.35±0.09	0.36±0.06	0.36±0.02	0.36±0.08
Disintegration	18.9 ± 0.4	19.1 ± 0.2	19.4 ± 0.5	19.5 ± 0.8	19.9 ± 0.4	20.2 ± 0.3	20.6 ± 0.8	20.7 ± 0.3
Drug content	99.8±0.43	99.6±0.39	99.5±0.26	99.2±0.41	99.2±0.28	98.9±0.27	98.6±0.58	98.4±0.31

[mean±SD, n=3]

CONCLUSION

This research manuscript clearly shows the successful development of the ODTs loaded with an antihypertensive drug namely propranolol hydrochloride. In this process of development of the ODTs, a novel superdisintegrant was also developed which enhanced the efficiency of the ODTs. It was unequivocally understood that cotton candy method can be a best option for the development of drug-loaded ODTs. This was enhanced bioavailability and the efficacy of the propranolol hydrochloride after preparation of ODTs. The drug loaded ODTs helped in the effective reduction of the drug entering the liver. This indeed can reduce the hepatic metabolism. In considering all these achievements, it can be concluded that this new form of oral drug delivery system can be ray of hope for scientists to deliver the drugs with high patient compliance.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

There is no conflict of Interest.

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