Formulation and Evaluation of Metoprolol Succinate Orodispersible Tablets Using Directly Compressible Coprocessed Excipient of Moringa Gum

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Abstract

Aims: The aim of the present research work is to develop fast-dissolving tablets of metoprolol succinate applying novel directly compressible coprocessed excipient which improves the functionality and masking the undesirable properties of the drug without any chemical modification. **Subjects and Methods:** For the development of coprocess excipient, synthetic superdisintegrants such as crospovidone, sodium starch glycolate (SSG), and croscarmellose sodium were processed with natural disintegrants Moringa gum in varying ratios 1:1–1:4. **Results:** Coprocessed excipient prepared from polymers ratio of 1:1 and 1:2 have shown good physicochemical properties and pre-compression parameters such as angle of repose, bulk density, true density, and compressibility index. The post-compression parameters have shown acceptable and within the pharmacopeial limit. *In vitro* drug release for all the formulations F1–F12 was found in between 95% and 97% and was satisfactory. The optimized batch F2 formulated with 4% Moringa gum and 2% SSG, the drug release was found to be 97% within 2 min. Developed optimized formulations were kept for stability study for 1 month as per the ICH guidelines and found to be stable. **Conclusions:** The study indicates that the use of coprocessed excipient has an added advantage over individual polymers and can be used in orodispersible tablet formulations irrespective of drug type.

Key words: Coprocessed excipient, fast-dissolving tablets, metoprolol succinate, moringa gum, natural disintegrants, orodispersible tablet

INTRODUCTION

ypertension is a chronic medical condition, in which the blood pressure in the arteries is elevated. Hypertension puts strain on the heart, leading to hypertensive heart disease and coronary artery disease if not treated. Beta-blocker is one of the drugs used to reduce hypertension. It works by making our heartbeat more slowly and with less force, thereby reducing blood pressure. Tablet is still the most popular dosage form among all existing forms due to ease of self-administration, compact in nature, easy to manufacture, and due to accurate in dosing. One main limitation of solid dosage form is difficulty in swallowing and chewing, particularly in geriatric and pediatric patients.^[1] The concept of orodispersible drug delivery system has emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate which cause to

release the drug as soon as they come in contact with saliva. Hence, the need for water during administration is not necessary that makes them highly attractive for pediatric and geriatric patients and in emergency conditions such as stroke, Parkinson's disease, and motion sickness. The European Pharmacopoeia adopted the term "orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing and it should disintegrate in <3 min.^[2] Nowadays, the pharmaceutical industries and formulators

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Received: 07-05-2019 **Revised:** 09-10-2019 **Accepted:** 21-10-2019 are widely oriented for the use of natural excipients, namely, emulsifier, stabilizer, gelling agent, granulating agent, suspending agent, binder, film former, disintegrants. Natural gums and mucilages are preferred over semi-synthetic and synthetic excipients in the field of drug delivery because they are cheap, easily available, biodegradable, biocompatible, and non-irritant in nature.

In rapid fast-dissolving tablets (FDTs) disintegration, the active substance comes into contact with the taste buds and the need for a pleasant taste for patient palatability. Hence, the taste-masking of bitter active substances is a critical hurdle for the successful approach of FDT formulations. To enhance patient compliance mainly in dissolving or disintegrating tablets which include sweeteners, flavors and the similar additives are not sufficient means for complete taste-masking. Recent advances in technology have presented viable dosage alternatives to taste-mask bitter drugs. Several approaches have been reported which involve complexation, freeze-drying, microencapsulation, fluidized bed coating, and supercritical fluids for taste-masking purposes.^[3]

Coprocessing is based on the novel concept of two or more excipients interacting at the subparticle level. The objective is to provide synergistic improvements as well as masking the undesirable properties of individual excipients. To produce tailor-made "designer excipients" to address specific functionality requirements, coprocessing ensures numerous possibilities.^[4]

The development of a coprocessed excipient involves the following steps. It initiates with the study of the material characteristics and functionality requirements by identifying the group of excipients to be coprocessed. Second, selection of the proportions or concentrations of various excipients followed by assessing the particle size required for coprocessed excipients have the multifold advantages which offered a single excipient with multiple functionalities such as removal of undesirable properties, overcome the limitation of existing excipients, improvement of organoleptic properties, production of synergism in functionality of individual components, reduction of industrial regulatory concern due to the absence of chemical change during coprocessing, and improvement in physicochemical properties.

Moringa oleifera is a small genus of quick growing tree distributed in India. The stem of the tree exudes a gum which is initially white in color but changes to reddish-brown or brownish-black on exposure to sunlight. It is sparingly soluble in water but swells in contact with water giving a highly viscous solution. It is a polyuronide consisting of arabinose, galactose, and glucoronic acid in the proportion of 10:7:2. The reports say about the application of *M. oleifera* gum as gelling, suspending agent, film former, binder, and release retardant in tablets. The gum has also got a high lethal dose in mice, indicating that it is safety to use. Considering these

utilities, this research work carried out for orodispersible metoprolol succinate formulation with the coprocessed excipients blended with natural polymer of Moringa gum.^[5]

SUBJECTS AND METHODS

Materials

Metoprolol succinate was obtained as a gift sample from Biocon, Bengaluru. Lactose was purchased from Suvidhinath Laboratories, Baroda. Crospovidone, croscarmellose sodium (CCS), sodium starch glycolate (SSG), and aspartame were purchased from Aman scientific products, Vijayawada. Sodium bicarbonate and microcrystalline cellulose (MCC) were purchased from Qualigens Fine Chemicals, Mumbai. Ethylcellulose and mannitol were purchased from Finar Chemicals Ltd., Ahmadabad, India. Moringa gum was collected and processed at Vikas Pharmaceutical Laboratory, Vissannapeta, India. All other ingredients used were of analytical grade.

Collection and purification of the Moringa gum

The *M. oleifera* tree gum was collected from the garden of Vikas Collage of Pharmacy. The gum was collected by making an incision of the tree stem, between 5 cm and 10 cm deep. A small plastic bag was hanged at the edge of the incision. It was left for 5 days after which the exudates were collected. More such incisions and collections were made to obtain enough quantity for this work.

After collecting the extrudes, they were dried, grounded, and passed through sieve 80#. Dried raw gum of 500 g was stirred in 2 L of distilled water continuously for 6-8 h at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washings were added to separate supernatant. The procedure was repeated 4 more times. Finally, the supernatant was made up to 500 ml and treated with twice the volume of acetone with continuous stirring to indicating complete precipitation and total separation from water. This process has removed organic compounds dissolved in the supernatant. The precipitated material was washed with distilled water and dried at 50-60°C under reduced pressure to obtain pure and exclusive Moringa gum. The dried purified gum was then pulverized and this was then weighed using a weighing balance to find out the percentage of yield.

Preparation of coprocessed superdisintegrants with natural polymer of Moringa gum

The coprocessed excipients were prepared by granulation method using different concentrations of moringa mucilage like 2–8%, respectively. The moringa mucilage (2% w/v) was formed by dispersing 200 mg of moringa in 10 ml of lukewarm

water. Similarly, 4, 6, and 8% w/v of mucilage were also prepared by following the same procedure. The mucilage of 2–8% was added to the various superdisintegrants (2%) such as SSG, CCS, crospovidone with MCC of 20% w/w, aspartame sodium (1% w/w), and mannitol q.s. until a damp mass was obtained. These damp masses were passed through #12 and the obtained granules were dried. The dried granules were passed through a series of mesh such as #10, #16, and #24, and the granules retained on 16# were collected and stored.^[6]

Formulation of orodispersible tablets by direct compression method

Metoprolol succinate orodispersible tablets were prepared by direct compression technique. The drug 20 mg was blended homogeneously for 10 min with coprocessed excipients of various ratio, talc (1%) and magnesium stearate (1%). To that, dry blend peppermint oil was sprinkled for organoleptic enhancement. The resultant mixture was compressed into tablets in 8 mm die cavities using Riddhi mini tablet press punching machine. Twelve formulations were prepared by varying the amount of the ingredients, as shown in Table 1.

Evaluation tests for orodispersible tablets

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. The orodispersible tablets of metoprolol succinate were evaluated for the following studies.^[7] The following preformulation studies were performed with metoprolol succinate dry blend with all formulation components.

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose " θ ." It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by the fixed funnel and free-standing cone method. An accurately weighed 5 g powders of metoprolol succinate were carefully poured into the funnel with its tips about 2 cm height (h) until the apex of the conical heap formed to be just reached the tip of the funnel. The mean diameter (r) and height were calculated and the angle of repose ($^{\circ}$) was calculated using the formula:

Angle of repose (°) = $tan^{-1}h/r$

Bulk density and tapped density

A quantity of 5 g of metoprolol succinate, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder of the tapped density apparatus maker of Campbell Electronics, Mumbai. The apparent volume (V_0) was observed and the cylinder was allowed to hit a height of 2.5 cm at 2 s intervals until there were no further changes in volume. Both bulk density (V_0) and tapped bulk density (V_c) were determined.

Carr's index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by,

$$I = 100x \frac{V_0 - V_f}{V_0}$$

Where " V_f " is the tapped density and " V_0 " is the bulk density of the powder.

Hausner's ratio

This indicates the flow properties of the powder and measured by the ratio of tapped density to the bulk density.

Physical evaluation tests

The tablets were tested for post-compression quality control tests such as hardness, friability, weight variation, and disintegration test.

Table 1: Composition of metoprolol succinate orodispersible tablets (F1–F12)				
Batch code	Drug:polymer ratio	Polymer ratio to total blend		
F1	1:2.5	2:2:20:1 (Moringa gum:SSG:MCC:aspartame)		
F2	1:2.7	4:2:20:1 (Moringa gum:SSG:MCC:aspartame)		
F3	1:2.9	6:2:20:1 (Moringa gum:SSG:MCC:aspartame)		
F4	1:3.1	8:2:20:1 (Moringa gum:SSG:MCC:aspartame)		
F5	1:2.5	2:2:20:1 (Moringa gum:CCS:MCC:aspartame)		
F6	1:2.7	4:2:20:1 (Moringa gum:CCS:MCC:aspartame)		
F7	1:2.9	6:2:20:1 (Moringa gum:CCS:MCC:aspartame)		
F8	1:3.1	8:2:20:1 (Moringa gum:CCS:MCC:aspartame)		
F9	1:2.5	2:2:20:1 (Moringa gum:crospovidone:MCC:aspartame)		
F10	1:2.7	4:2:20:1 (Moringa gum:crospovidone:MCC:aspartame)		
F11	1:2.9	6:2:20:1 (Moringa gum:crospovidone:MCC:aspartame)		
F12	1:3.1	8:2:20:1 (Moringa gum:crospovidone:MCC:aspartame)		

CCS: Croscarmellose sodium, MCC: Microcrystalline cellulose

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Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shock of handling in manufacture, packaging, and also in shipping. The hardness was tested for five tablets from each formulation batch using Monsanto hardness tester and the average of the three is reported. It is expressed in kg/cm².

Friability testing

As specified in the United States Pharmacopeia (USP), weight variation test was run by taking 10 tablets. The weight (W1) of those tablets was determined before redusted before weighing. The tablets were then placed in a test drum of friability tester "FR1000" of Copley Scientific, Mumbai, India, and allowed to rotate for 100 times. The tablets were reweighed (W2) having first removed accumulated dust to them. The result was calculated in terms of percentage weight loss by utilizing the following formula.

Friability (%) =
$$\frac{W1 - W2}{W1} \times 100$$

The maximum weight loss not more than 1% is normally acceptable.

Weight variation test

Twenty tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight.

% Deviation =
$$\frac{-\text{individual tablet weight}}{\text{Average weight of tablet}} \times 100$$

The maximum weight variation not more than 7.5% is normally acceptable for the tablets weigh between 80 mg and 250 mg.

Uniformity of drug content

Randomly selected five tablets were powdered from each formulation. The quantity equivalent to single dose of the drug was dissolved in 50 ml buffer solution of pH 6.8 for 5 h with occasional shaking. After filtration to remove insoluble residue if any, 1 ml of the filtrate was diluted to 10 ml with the buffer. The absorbance was measured at the required λ max using an ultraviolet (UV)–visible spectrophotometer. The experiments were carried out in triplicate for all formulations and average values were recorded.^[8] The drug content was calculated using the following equation.

% Drug content = Conc. (
$$\mu$$
g/ml) × Dilution factor × $\frac{100}{50}$

Disintegration test

To test for disintegration time, one tablet was placed in each tube, and the basket rack was positioned in a 1 L beaker of

medium at $37 \pm 2^{\circ}$ C. The standard motor-driven device was used to move the basket assembly containing the tablets up and down through a distance of 5–6 cm at a frequency of 28–32 cycles/min. Perforated plastic discs were placed on top of the tablets.

In vitro drug release studies

In vitro dissolution studies were performed in a USP XXIII dissolution test apparatus, type II (paddle method) (Disso 2000, Lab India, India) at 37 ± 0.5 °C and with a paddles rotation speed of 50 rpm.^[9] The formulated tablets were placed into 900 ml of phosphate buffer solution (pH 6.8) as the dissolution medium. The tablets were placed in 316 stainless steel sinkers which kept them in sink condition during the dissolution study. Dissolution studies were carried out in triplicate. Ten milliliters aliquots of samples were collected at 5 min interval up to 30 min. They were filtered and estimated for metoprolol succinate release using UV-visible spectrophotometer at 274 nm. At each time of withdrawal, 10 ml of fresh medium was replaced into the dissolution flask. The concentrations were calculated using the standard calibration curve prepared using 6.8 phosphate buffer as solvent.

Mechanism of drug release

To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models as follows:^[10]

- 1. Zero order: Cumulative percentage of drug released versus time
- 2. First order: Log cumulative percentage of drug remaining versus time
- 3. Higuchi: Cumulative percentage of drug released versus square root of time
- 4. Korsmeyer–Peppas: Log cumulative percentage of drug released versus log time.

The linearity of the plots was obtained from the values of regression coefficient (R^2). The model with the highest linearity (R^2 value approaching unity) was chosen as the best fit kinetic model.

Accelerated stability studies

Short-term accelerated stability testing was carried out according to the ICH guidelines considering $40 \pm 2^{\circ}C/75 \pm 5\%$ relative humidity in a stability chamber for a period of 1 month. The orodispersible tablets of optimized formulation were subjected to stability studies at both initial evaluation and at the end of the 1st month of the tablets exposed to stability chamber were again analyzed for their physical appearance, assay (%), and *in vitro* drug release profile at 5th, 10th, and 20th min.

RESULTS

Evaluation of pre-compression parameters

Pre-compressed powder blend was studied by performing tests angle of repose, bulk density, tapped density, compressibility index, and Hausner ratio and cited in Table 2.

Angle of repose

The angle of repose found to be within the limit of $20.22 \pm 0.24-27.12 \pm 0.22$ which indicated excellent flow.

Bulk density

The bulk density of all formulation was found in the range of 0.262 ± 0.02 – 0.288 ± 0.03 g/cc. It is within the acceptable limits.

Tapped density

The tapped density of all formulation was found in the range of 0.262 ± 0.02 – 0.288 ± 0.03 g/cc. It is within the acceptable limits.

Compressibility index

Carr's index was found to vary from 15.73 to 19.27, which indicated good flowability and fair compressibility.

Hausner's ratio

The result of the Hausner's ratio of all formulations was found between 1.19 and 1.24 which indicates good flow behavior of formulation blend.

Physical evaluation of oral dispersible tablets

The tablets were tested for post-compression quality control tests^[11] such as hardness, friability, weight variation, and disintegration test. The results are shown in Table 3.

Hardness

The hardness of the tablets of all formulations was within the range of $3 \pm 0.03-4.1 \pm 1.17$ kg/cm². The result indicates that all the formulated tablets pass the test.^[12]

Friability

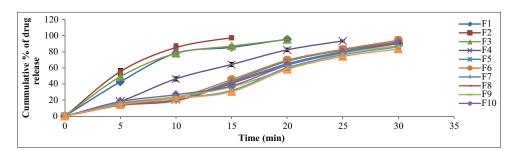
The result revealed good adhesion of tablet ingredients. Hence, all the formulated tablets pass the test.

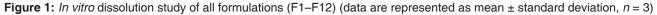
Content uniformity

As per the IP, the content uniformity should be in the range of 85–100%. The results showed that the percentage of metoprolol succinate was ranging from 87% to 98% in all the

Table 2: Evaluation of pre-compression parameters					
Batch code	Angle of repose (X±SD)	Bulk density (g/cc) (X±SD)	Tapped density (g/cc) (X±SD)	Hausner ratio	Compressibility index (Carr's index)
F1	20.34±0.04	0.224±0.03	0.274±0.04	1.22	18.25
F2	21.32±0.12	0.226±0.02	0.272±0.03	1.20	16.91
F3	20.42±0.08	0.225±0.03	0.267±0.01	1.19	15.73
F4	20.52±0.61	0.239 ± 0.02	0.288±0.03	1.21	17.01
F5	20.47±0.22	0.222±0.03	0.275±0.02	1.24	19.27
F6	24.28±0.34	0.235±0.02	0.279±0.01	1.19	15.77
F7	23.56±0.41	0.234±0.01	0.282±0.03	1.21	17.02
F8	25.28±0.26	0.237±0.02	0.286±0.02	1.21	17.13
F9	20.22±0.24	0.219±0.05	0.262±0.02	1.20	16.41
F10	24.8±0.14	0.232±0.05	0.277±0.01	1.19	16.25
F11	23.16±0.62	0.234±0.04	0.279±0.03	1.19	16.13
F12	27.12±0.22	0.237±0.02	0.286±0.02	1.21	17.13

Data are represented as mean (X)±standard deviation (SD), n=3





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Table 3: Post-compression studies of metoprolol succinate tablets formulated with coprocessed Moringa gum					
Batch code	Weight variation (mg) (X±SD)	Hardness (kg/cm²) (X±SD)	Friability (%) (X±SD)	Drug content (%) (X±SD)	Disintegration (s) (X±SD)
F1	196±0.2	3±0.03	0.34±0.02	89.92±0.02	47±3
F2	198±0.5	3.5±0.04	0.33±0.03	92.03±0.02	36±4
F3	208±0.5	4±0.03	0.33±0.05	95.56±0.01	44±12
F4	204±0.5	3±0.05	0.44±0.11	87.95±0.01	63±9
F5	205±0.2	3±0.04	0.42±0.2	93.29±0.02	55±8
F6	189±0.6	4±0.03	0.37±0.12	95.0±0.02	43±7
F7	187±0.4	4.1±1.17	0.43±0.16	98.25±0.01	54±15
F8	199±0.6	4±1.25	0.42±0.08	97.81±0.03	83±8
F9	209±0.4	3.8±1.1	0.35±0.1	93.75±0.02	56±4
F10	207±0.2	3±0.04	0.42±0.6	90.7±0.01	43±6
F11	212±0.5	4±0.02	0.33±0.2	98.73±0.03	54±15
F12	205±0.4	3.1±1.7	0.41±0.15	95.21±0.02	68±12

Data are represented as mean (X)±standard deviation (SD), n=3

Table 4: Accelerated stability studies report of orodispersible tablet					
Period	Dissolution (%)			Assay (%)	Appearance
	5 min	10 min	20 min		
Initial	55.4±1.2	85.5±2.3	97.9±2.6	96.13±3.2	Off white
Final (1 Mo)	54.3±1.4	84.1±3.2	97.7±1.5	95.44±2.4	Off white

Data are represented as mean±standard deviation, n=3

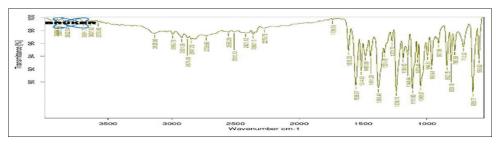


Figure 2: Infrared spectrum for metoprolol succinate

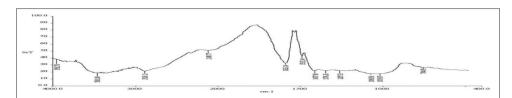


Figure 3: Infrared spectrum for gum Moringa gum

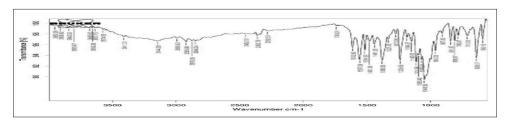


Figure 4: Infrared spectrum of optimized formula (F2) of metoprolol succinate with coprocessed Moringa gum

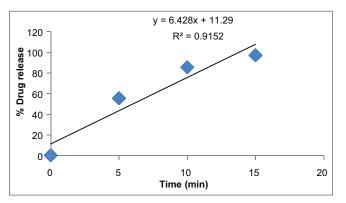


Figure 5: Zero-order drug release of metoprolol succinate with coprocessed Moringa gum in F2

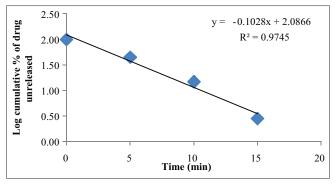


Figure 6: First-order drug release of metoprolol succinate with coprocessed Moringa gum in F2

formulations. The result revealed that the drug is uniformly dispersed in the formulations and confirms the homogeneous mixing of the drug and polymer.^[13]

Weight variation test

All the formulated tablets were showing within 5% deviation. The result indicated that all the formulated tablets pass the test.

Disintegration test

The disintegration time of formulated batches has shown in the range of 36-83 s. Among all the formulation batches, formulation F2 has shown least disintegration time of 36 s.

Drug release study of metoprolol succinate tablets formulated with coprocessed Moringa gum

To conform and optimize the orodispersible tablets of batches F1–F12 were evaluated for release of metoprolol succinate in the dissolution medium of phosphate buffer solution (pH 6.8). Immediate release profile was studied at 5, 10, 15, 20, 25, and 30 min. The graphical release pattern is displayed in Figure 1. The cumulative percentage of metoprolol succinate released from orodispersible tablets was repeated 3 times (n = 3). From the above studies, it was concluded that the release rate of F2 has shown a steady immediate release within 15 min.^[14]

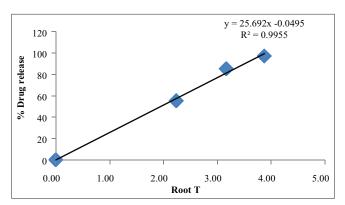


Figure 7: Higuchi graph of drug release of metoprolol succinate with coprocessed Moringa gum in F2

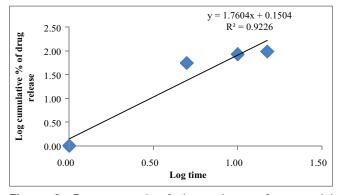


Figure 8: Peppas graph of drug release of metoprolol succinate with coprocessed Moringa gum in F2

Drug-excipient interaction studies

Drug-excipient interaction studies were performed using Fourier transform infrared (FTIR) spectrophotometer.^[15] The FTIR spectra for the formulation and pure drug are shown in Figures 2-4. Characteristic peaks obtained for the pure drug correlated well with that of the formulation peaks. These indicated that the drug was compatible with the formulation components and there were no chemical interactions between the metoprolol succinate and coprocessed Moringa gum.^[3]

Accelerated stability study of the best batch

The accelerated stability study report of metoprolol succinate with coprocessed Moringa gum revealed that the formulation has not undergone any physical or chemical degradation during the period. There was no significant change in the in vitro drug release and drug assay at an interval of 1 month, as shown in Table 4.

Pharmacokinetic report

Based on mathematical data revealed from models, from Figures 5-8, it was concluded that the release data were best fitted with the first order and Higuchi equation. Higuchi equation explains the fast release mechanism, the diffusion exponent "n" values were found to be more than 0.5 for the metoprolol succinate tablets indicating non-Fickian diffusion.

Based on the statistical analysis, it was concluded that the calculated $F_{(2,8)}$ value between columns was found to be 1.45 which is more than the tabulated value at 5% significant level, i.e., P < 1.15. Hence, the null hypothesis was rejected; therefore, it was found that there is a significant difference between the natural polymer ratios in coprocessed technique (1:1, 1:2, 1:3, and 1:4).

The calculated $F_{(2,8)}$ value between the rows was found to be 0.45 which is far less than the tabulated $F_{(2,8)}$ value at 5% significant level, i.e., P > 1.15. Hence, the null hypothesis was accepted. Therefore, it was found that there is no significant difference between the natural polymers blended with synthetic polymers using coprocessed technique.

CONCLUSIONS

The drug selected for the present investigation was metoprolol succinate; a β selective adrenergic blocking agent is an orally active antihypertensive agent. The natural polymer chosen for the present investigation was Moringa gum a natural and high-molecular-weight heteropolysaccharide gum. Twelve formulations were prepared by varying the concentration of polymers using a coprocessed technique with the natural polymer Moringa gum and superdisintegrants such as SSG, crospovidone, and CCS which retard the drug release over a period of time compared with highly rate synthetic polymer. Those formulations were subjected to various evaluation parameters such as melting point, FTIR, pre-compression parameters, post-compression parameter like in vitro drug release studies and kinetic release. It was further observed that, by increasing the polymer concentration, the drug release was increased. The FTIR spectra revealed that there was minor interaction between polymers and drug which concluded that polymers were compatible with metoprolol succinate. Flow properties such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose shown satisfactory results. Formulated tablets were found to be for various physical properties such as tablet hardness, weight variation, friability, content uniformity, and in vitro drug release. In vitro drug release of metoprolol succinate tablets shown fast release pattern, which may be attributed to the using various concentrations of natural polymers and synthetic polymer. Based on the results obtained, the F2 (6% of SSG with Moringa gum) was considered as the optimum formulation to design fast drug delivery system for quick onset of action.

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