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Formulation and Evaluation of Fast Disintegrating Oral Tablets of Ibuprofen using Mannitol, PEG 4000, Cellactose and Sodium Starch Glycolate via Direct Compression

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ABSTRACT

Background: The needs for improve drug bioavailability has led to the development of new excipients and combination of existing excipients to yield the desired purpose. This study seeks to develop an orally fast dissolving mouth disintegrating tablet of ibuprofen using PEG 4000, mannitol, cellactose and sodium starch glycolate as a preferred alternative for patient compliance and easy administration to geriatric patients.

Method: Ten batches (A1, A2, A3, B1, B2, B3, C1, C2, C3, D1, D2, & D3,) of mixture of drug and various excipients combinations were developed and evaluated for powder properties. Tablets, equivalent of 500 mg of all the batches were compacted by direct compression method, on a Cadmach rotary tableting machine using 12.5 mm round-faced punches with pressure load of 10 KN. The compressed MDTs were evaluated for friability, weight variation, hardness, content uniformity, disintegration time, in vitro drug release and tablet oral taste.

Results: The results of powder flow properties and tablets analysis for all batches A – D, batch A3, B1, B2, B3, and C1 showed promising characteristics for an ideal MDT with average powder flow rate, tablet disintegration time, T90%, crushing strength and taste as follow: A3 (1.58 gs-1, 2.09 s, 115 N, 7.5 min. and acceptable taste) respectively; B1 (1.54 gs-1, 2.01 s, 60 N, 6.5 min. and slight bitterness) respectively; B2 (1.58 gs-1, 1.52 s, 60 N, 5.5 min. and slight bitterness) respectively; B3 (1.61 gs-1, 1.05 s, 40 N, 5.0 min. and slight bitterness) respectively; C1 (1.72 gs-1, 0.57 s, 55 N, 4.0 min. and acceptable) respectively. Based on these characteristics, formulation batch C1 is more qualified for formulation of fast dissolving MDT.

Conclusion: The fast-disintegrating oral tablets of batch C1 possessed the ideal characteristics for physical stability and rapid release of API which is an indication of improved bioavailability.

1. Introduction

Mouth disintegrating tablets (MDTs), also known as orally disintegrating tablets (ODTs), fast dissolving (FDTs), quick dissolving (QDTS), fast disintegrating tablets (FDTs) and orodispersible systems (ODTs), possessed the unique property of disintegrating in the mouth in few seconds without chewing and the need of water and are thus helped to improve patient compliance. A mouth disintegrating tablet (MDT) is defined as a solid dosage form that dissolves or disintegrates quickly in the oral cavity without the need for administration of water. The European Pharmacopoiea describes ODTs/MDTs as uncoated special tablets designed to be placed in the mouth purposely to disperse quickly for rapid absorption and as tablets which should disintegrate within 3 minutes[1]. FDA defines MDT as

a solid dosage form which disintegrates quickly within a few seconds when placed upon the tongue [2]. Mouth disintegrating tablets could be a better replacement for conventional solid oral dosage forms (capsules and tablets) in pediatric, geriatric, bedridden, nauseous or non-compliant patients [3]. Immediately after coming in contact with saliva MDTs disintegrate quickly and yielding a suspension that can be easily swallowed or absorbed by the patient [4]. The API now in suspension could swiftly be absorbed through the pre-gastric route from the mouth, pharynx and esophagus and through gastrointestinal epithelium to elicit the desired effect [5]. MDTs have also been found to be the dosage form of choice for patients suffering from nausea, vomiting or motion sickness [6]. Reasons for patient acceptance of MDTs include its oral disintegration, good mouth-feel, easy handling, easy swallowing, no need of water and effective taste masking.

The formulation and development of pharmaceutical drug into a novel and highly functional dosage form like MDT affords pharmaceutical companies to enjoy market exclusivity [7]. Formulation of this dosage form helps to improve the solubility of poorly water soluble drugs and it helps increase the bioavailability of such drugs [8]. There are few obstacles involved in the formulation and development of MDTs [3,9]. These include difficulties in: achieving mechanical strength, fast disintegration of tablets, acceptable taste for patient compliance and selection of ideal excipients for the formulations.

Taste masking is the first and foremost task in the formulation of MDTs. Conventional methods like direct compression, wet granulation, moulding, spray-drying, freeze-drying and sublimation were used to prepare ODTs/MDTs. New advanced technologies like Quick-Disc

Table 1: Percentage Composition of component per batch

Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3	D1	D2	D3	Function
Ibuprofen (mg)	100	100	100	100	100	100	100	100	100	100	100	100	Anti - inflammatory
Mannitol (mg)	200	185	160	-	-	-	150	140	130	-	-	-	Additive/Excipient
PEG 4000 (mg)	-	-	-	150	140	130	50	45	30	50	45	30	Additive/Excipient
Cellactose (mg)	200	210	220	200	210	220	200	210	220	200	210	220	DC Excipient
Sorbitol (mg)	-	-	-	50	45	30	-	-	-	150	140	130	Additive/Excipient
Sod. Starch Glycolate (mg)	10	15	30	10	15	30	10	15	30	10	15	30	Disintegrant
Colloidal silicon dioxide (aerosol)(mg)	2	2	2	2	2	2	2	2	2	2	2	2	Glidant/Lubricant
Anhydrous citric acid (mg)	8	8	8	8	8	8	8	8	8	8	8	8	Flavouring Agent/Taste enhancer. Stabilizer
Total (mg)	520	520	520	520	520	520	520	520	520	520	520	520	

2.2.2 Angle of repose of powder mixture

Angle of repose is the maximum angle possible between the surfaces of a pile of powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose with the following equation:

$$tan\ \theta\ =\ h/r. \qquad Equation\ 1$$

Where θ is the angle of repose, h stands for the height of the pile, and r represents the radius of the base of the pile [12].

2.2.3 Bulk Density and Tapped Density of Powder Mixtures

A suitable amount of powder from each formulation was lightly shaken to break agglomerates and introduced into a 10 mL measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. Bulk density (Db) and tapped bulk density (Dt) were calculate using following formula [13]:

2.2.4 Carr Index of Powder Mixtures

The compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the Db and Dt of a powder and the rate at which it packed down. The formula for Carr index is as below:

$$\text{Cars index} = Db - Dt / Db \qquad \textit{Equation 2}$$

Where Dt is tapped density of the powder and Db is bulk density of the powder.

2.2.5 Hausner's Ratio of Powder Mixtures

It is determined by comparing the tapped density to the bulk density and it is expressed in Equation 3

$$\text{Hausner ratio} = \frac{Dt}{Db} \qquad \textit{Equation 3}$$

2.3 Evaluation of Compressed Tablets of MDT

2.3.1 Weight Variation

The test was performed according to specifications given in the USP. Randomly, 20 tablets were selected after compression and the average weight was determined. None of the tablets deviated from the average weight by more than ± 5% [14].

2.3.2 Friability Test

This test was performed to determine the effects of friction and shock. Preweighed sample of 10 tablets (w_o) was placed in the Erweka friabilator and rotated at 25 rpm for about 4 minutes. The tablets were dedusted and reweighed (w_1), and the friability percentage was calculated using equation. Compressed tablets should not lose more than 1% of weight [15].

$$\text{Friability\%} = [wo - w1] / wo \times 100 \qquad \textit{Equation 4}$$

2.3.3 Hardness Test

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The hardness of the tablets was determined by diametral compression using Erweka hardness tester [16].

2.3.4 Thickness Test

The thickness was measured by placing tablet between two arms of the vernier callipers. Five tablets were taken and their thickness was measured individually. The mean was determined [15].

2.3.5 Disintegration Time

The *in vitro* disintegration studies were carried out using a Digital Tablet Disintegration test Apparatus (Erweka ZTGermany). One tablet was placed in each of the six tubes of the basket assembly and then disk was added to each tube. This assembly was then suspended in a one-litre beaker containing 900 mL phosphate buffer solution (pH 7.4) with its temperature being maintained at 37±2 ºC. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for complete disintegration of the tablet was recorded [13].

2.3.6 Content Uniformity

Ten tablets of each formulation were crushed and powder equivalent to 1mg of Ibuprofen was suspended in approximately 50 mL of 0.1 N HCl and shaken for 15 minutes. Final volume was adjusted to 100 mL with 0.1 N HCl and filtered (Whatman No.1 filter paper). After serial dilution the absorbance of final solution was recorded ibuprofen content at 264 nm using UV/Vis spectrophotometer against a reagent blank and the content was compared from a calibration curve prepared with standard Ibuprofen in 0.1 N HCl [13].

2.3.7 Preparation of ibuprofen calibration curve

Hundred milligram (100 mg) of ibuprofen was accurately weighed using an analytical balance (AWS, USA), transferred to a 100 ml volumetric flask containing 10 mL of phosphate buffer pH 7.4. The powder was dispersed and made up to volume with the phosphate buffer to give the stock solution. From the stock solution, final concentrations of 2, 4, 6, 8, 10, and 12 µg/ml were prepared in 100 mL volumetric flask. Then the absorbance of the resulting solutions were measured spectrophotometrically at λ max of 264 nm using the phosphate buffer as blank using GS-UV

61PC double beam Spectrophotometer (General Scientific, India). Then, the absorbance versus concentration of solutions were plotted to obtain the calibration curve.

2.3.8 In vitro Dissolution of Ibuprofen from the Mouth Disintegration Tablets

Six tablets of each formulation were used in the dissolution experiments. The dissolution rates of pramipexole were determined in USP 24 type II apparatus (paddle method, Erweka DT 6RGermany) at 37± 0.5°C ºC in 900 mL phosphate buffer solution (pH 7.4) with the rotation speed of 50 rpm. At appropriate time intervals (0, 5, 10, 15, 20, 25, and 30 minutes), 5 mL of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. The samples were analysed for Ibuprofen at 264 nm. . The dissolution data obtained was plotted as percent cumulative drug released versus time [13]

2.3.9 Taste evaluation of the formulated MDT (Panel method)

Physiologically, taste is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. There are four basic type of taste; salty, sour, sweet and bitter.

Both ethical approval for this aspect of research and consent of the volunteers were documented. UIL/FPS/ERC05

The taste of some selected formulations of mouth disintegrating tablets was checked by panel method. The study protocol was explained and written consent was obtained from the volunteers. Six healthy male volunteers were randomly selected. The control was the pure drug. Prepared tablets were placed in the mouth by each volunteer and the bitterness level was recorded against pure drug using a numerical scale (classifying bitter taste into five levels: level 0: tasteless, level 1: acceptable bitterness, level 2: slight bitterness, level 3: moderately bitterness and level 4: strong bitterness) (Table 2)

Table 2: Taste Characteristics with their Corresponding Panel Scores

Taste characteristics	Score
Level 1: No bitterness	0
Level 2: Threshold /acceptable bitterness	1
Level 3: Slight bitterness	2
Level 4: Moderate bitterness	3
Level 5: Strong bitterness	4

2.3.10 Statistical Analysis

All data obtained were expressed as Mean ± Standard Deviation. The data obtained from the taste panel test was evaluated using one-way analysis of variance (ANOVA). The level of significance was set at $p < 0.05$.

3. Results

3.1. Powder Flow Properties

The Powder flow properties were analyzed and shown in Table 3. For all of the formulations Carr's index were obtained in the range of 20.25 to 27.24 % and Hausner's ratio were 1.25 to 1.37 which indicated good compressibility and flow-ability.

3.2. Tablet Properties

The tablets were prepared using the direct compression method. All of the formulations passed the weight variation test. The hardness of all tablets was found in the range of 40.0 $\pm$ 0.0 to 115.0 $\pm$ 3.0 N. Friability was observed to be in the range of 0.01 to 1.04 % (Table 4) which was an indication of good resistance of the tablets to abrasion or shock due to transportation. Disintegration times varied from 0.57 sec. to 6.50 min. According to these results (Tables 3) and based on compressibility index, crushing strength, disintegration time, and friability values, formulations A3, B1, B2, B3 and C1 were selected for optimization studies (Table 4).

Table 3: Physicochemical properties of various powder mixtures

Formu-lation	Bulk Density g/ml	Tapped density g/ml	Flow rate gs^{-1}	Angle of repose (°)	Compress-ibility index (%)	Hausner ratio	Flow Property
A1	0.441	0.553	1.43	31.20	20.25	1.25	Good
A2	0.426	0.553	1.67	32.08	22.97	1.29	Good
A3	0.429	0.577	1.58	33.70	25.65	1.35	Good
B1	0.454	0.624	1.54	30.30	27.24	1.37	Good
B2	0.468	0.625	1.58	31.32	25.12	1.34	Good
B3	0.487	0.629	1.61	27.89	22.58	1.29	Good
C1	0.451	0.577	1.72	32.90	21.84	1.28	Good
C2	0.451	0.590	1.54	29.90	23.56	1.31	Good
C3	0.445	0.605	1.45	33.90	26.45	1.36	Good
D1	0.496	0.676	1.54	32.90	26.63	1.36	Good
D2	0.487	0.630	1.49	35.30	22.70	1.29	Good
D3	0.490	0.633	1.38	28.80	22.59	1.29	Good

All values represented above are means of three readings.

The powder mix batch C1 shows the flow and compressibility characteristics as shown in Table 3. Flow rate of 1.72 gs^{-1} and compressibility value as 21.84 % indicates good flow property.

Table 4: Compact properties of compressed tablets for batches A to D

Batch	Tab wt (g)	Tab. Diameter (mm)	Tab. Thickness (mm)	Tab. Crushing Strengh (N)	Disintegration (s)	Friability (%)	Content uniformity (%)	$T_{45\,\%}$ (min)	$T_{90\,\%}$ (min)
A1	0.52 ±0.02	12.78	3.54	65 ± 1.0	4.25 ±0.03	0.98	98.0± 1.5	5	14
A2	0.52 ±0.04	12.80	3.30	113 ±2.5	3.28 ±0.02	0.92	99.0± 0.5	5	13
A3	0.52 ±0.01	12.83	3.54	115 ±3.0	2.09 ±0.01	0.19	98.5± 0.5	4	10
B1	0.52 ±0.04	12.85	3.53	60 ±0.0	2.01 ±0.01	0.01	97.5± 1.5	4	7
B2	0.52 ±0.01	12.80	3.53	60 ±0.5	1.52 ±0.02	0.01	99.0± 0.0	3	8
B3	0.52 ±0.02	12.82	3.60	40 ±0.0	1.05 ±0.00	0.01	98.7± 1.0	3	6
C1	0.52 ±0.01	12.80	3.60	55 ±0.5	0.57 ±0.01	1.04	99.0± 1.0	3	5
C2	0.52 ±0.03	12.80	3.35	115 ±3.0	3.25 ±0.05	0.29	99.0± 0.5	5	11
C3	0.52 ±0.03	12.80	3.40	115 ±2.9	3.10 ±0.02	0.86	97.6± 2.0	5	12
D1	0.52 ±0.01	12.74	3.54	90 ±0.0	6.05 ±0.04	0.29	98.6± 1.2	5	15
D2	0.52 ±0.02	12.72	3.50	65 ±2.5	6.50 ±0.04	0.39	99.5± 0.0	5	15
D3	0.52 ±0.02	12.76	3.60	70 ±1.5	5.23 ±0.02	0.01	98.9± 0.1	5	15

All values represented above are means of three readings.

Table 5: Taste Characteristics with their Corresponding Panel Scores

Formulation code	No bitterness Score= 0	Threshold bitterness Score= 1	Slight bitterness Score = 2	Strong bitterness Score = 4
A1		1		
A2		1		
A3		1		
B1			2	
B2			2	
B3			2	
C1		1		
C2		1		
C3		1		
D1			2	
D2			2	
D3			2	
Pure Ibuprofen (API)				4

Most volunteers reported the lowest bitterness level (threshold/acceptable) for the prepared MDTs of C1 to C3 when compared with the pure ibuprofen on the proposed numerical scale. This indicates that MDT of batches C1 to C3 are qualified for oral dispersion and absorption (Table 5)..

Calibration Curve of Ibuprofen

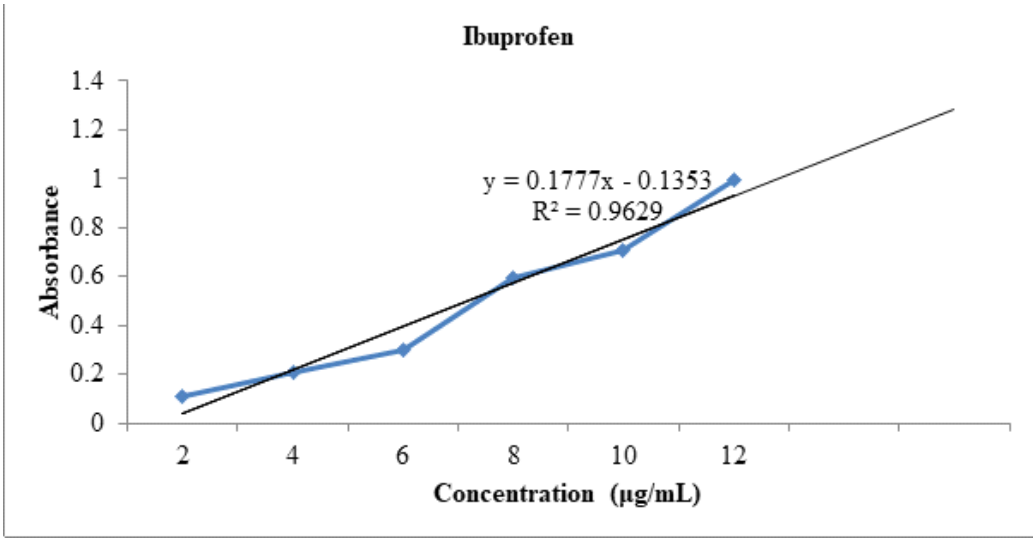

Figure 1: Calibration curve of ibuprofen

The concentration of 2, 4, 6, 8 10 & 12 µg/ml respectively, the absorbance was measured at 264 nm against blank by using UV- spectrophotometer.

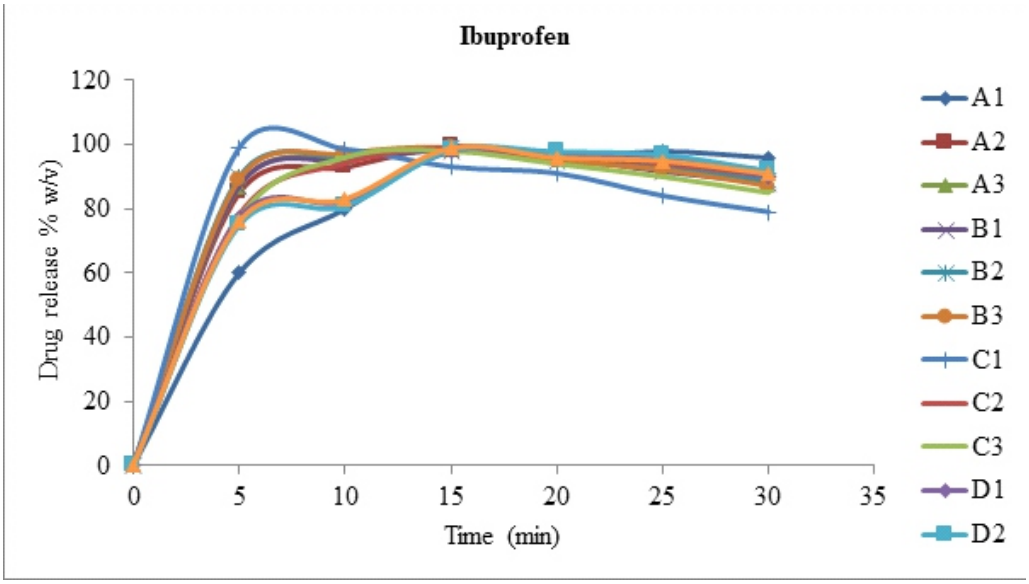

Figure 2: Percentage of Ibuprofen released from ODT against time in minutes.
The T90 % for A3, B1, B2, B3, and C1 are: 7.5, 6.5, 5.5, 5.0 and 4.0 minutes respectively.

4. Discussion

The incidence of rheumatoid arthritis and osteoarthritis are related to aging and mostly developed in elderly peoples with difficulty in walking, and migraine and dysmenorrhea common in young and middle aged patients. Thus, the development of the MDT of ibuprofen could be a preferable alternative to conventional oral route, in improving the bioavailability, quality of life and patient acceptability. In the current study MDT of ibuprofen was designed, formulated and evaluated varying the amount of mannitol, PEG 4000 and sodium starch glycolate (super-disintegrant) to see the effects of using this different excipient on vital physical properties of the tablets required for MDT according to European Pharmacopoeia. The proper selection of specialize vehicles and their consistency of performance is of importance to the formulation of a fast disintegrating oral dosage form. Here, we performed a preliminary study to choose the best ratio of mannitol, PEG 4000, sorbitol and sodium starch glycolate. Based on the results (Table 3), formulations A1 – A3 without PEG 4000 yielded compacts with higher crushing strength ranging from 65 N – 115 N, disintegration time 2.09 – 4.25 min. and friability, 0.19 – 0.98 %. Formulations B1 –B3 without mannitol (Table 3) produced compacts with moderate crushing strength range of 40 – 60 N, disintegration time of 1.05 – 2.01 min. and friability 0.01 % for the three batches. Formulations C1 – C3 yielded compacts with crushing strength 55 – 115 N, disintegration time 0.57 – 3.10 min. and friability 0.29 – 1.04 %. It was discovered that batches containing mannitol were stronger than those without it as reflected by their crushing strength and friability values. Inclusion of cellactose serves two functions in all formulations. Firstly, it aided direct compression and secondly, it improved the disintegration of all formulations featuring this excipient. PEG 4000 is a solubility aided excipient which also helps to improves water penetration and disintegration of every tablet containing it as well as reducing the hardness of such compact due to it nature.

Disintegration time is one of the main criteria in MDTs. They should be rapidly disintegrated in buccal cavity without need for water. Based on European Pharmacopoeia, formulation 'C1' is the best compact with ibuprofen, mannitol, PEG4000, cellactose and SSG as 100 mg, 150 mg, 50 mg, 200 mg and 10 mg respectively. The physical characteristics of compacts formed for the C1 in terms of crushing strength, disintegration, friability, content uniformity, and drug release, were 55 N, 0.57 min., 1.04 %, 99 % (Table 5) and T90 % as 4 min. (Fig. 2) respectively. The drug content was completely released from all of the formulations within 15 min which would contribute to higher bioavailability of ODT compared to conventional form.

The taste panel results showed that formulations C1 – C3 presented lowest or acceptable bitter taste due to the masking and suiting effects of mannitol (Table 5). The

introduction of MDTs has solved some of the problems encountered in administration of drugs to paediatric and elderly patients, who constitute a large proportion of the world's population. Large numbers of companies are in the MDT drug delivery market, which is evident from the number of products launched as MDTs and of patents approved. Amongst other drug delivery companies, those in the MDT market possess a tremendous potential of extending the drug product life cycle and extending the profitability of existing products. Due to the flexible nature of MDT, several doses of molecules of wide variety of chemical drugs can be incorporated into the dosage. The creative technologies include fine particle coating or addition of flavours/sweeteners into the tablet matrix for taste masking, granulation, spray-drying, freeze-drying and moulding. These methods are now widely accepted in the industry for developing MDTs. It is now certain that future trends in drug delivery system innovation will continue to employ different technological ideas to create novel technologies.

5.0. Conclusion

In the current study we are able to design, prepare, and evaluate MDT of ibuprofen to improve the bioavailability, quality of life and patient acceptability for patients with dysmenorrhea, inflammation, and geriatric patients with osteoarthritis, and rheumatoid arthritis. The flow properties of the drug and the excipients were good in all of the formulations. The overall results suggest that the MDT tablets of ibuprofen according to formulation C1 met the EU standard requirement for such a fast release dosage forms. We conclude that this batch is a good candidate for future development into highly functional and acceptable bioavailable mouth disintegrating tablet for children, geriatric, and special medical conditions requiring rapid drug release reaching in the blood at desirable time. .

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