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Studies on rapidly disintegrating tablets containing taste masked venlafaxine polymer complex

Jayshree S. Hadke, Shagufta Khan* and Dilesh J Singhavi

Institute of Pharmaceutical Education and Research (IPER), Borgaon (Meghe), Wardha, Maharashtra, India

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ABSTRACT

Venlafaxine is a phenethylamine bicyclic derivative chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents, having bitter taste. Thus, in the work undertaken, an attempt was made to mask the taste by complexing venlafaxine HCl with Eudragit EPO and to formulate into a rapid disintegrating tablet. The drug polymer complexes were prepared using precipitation method by taking drug: Eudragit EPO ratios 1:1, 1:2, 1:2.5, 1:3, 1:3.5 and 1:4. The drug polymer complexes were evaluated for the drug content, Fourier transform infrared spectroscopy , X-ray diffraction, in-vitro and in-vivo taste evaluation. The optimum drug: polymer ratio was selected based on in-vitro taste evaluation. Rapid disintegrating tablets (RDTs) were developed from optimum drug: polymer ratios of 1:3. RDTs were evaluated for hardness, tensile strength, friability, weight variation, drug content, wetting time, water absorption ratio, in-vivo disintegration time, in-vivo disintegration time, and sensory evaluation of roughness and taste evaluation. RDTs prepared using spray dried lactose, spray dried mannitol and microcrystalline cellulose in the ratio 1:1 and 8 % w/w crospovidone XL-10 (F4), showed faster disintegration (within 8 sec.) and complete bitter taste masking of Venlafaxine. Human volunteers rated formulation F4 non-bitter with score 0. Tablets of batch F4 also revealed rapid release ($t_{90,}$ 60 sec) in simulated gastric fluid. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity with improved dissolution

Key words: Venlafaxine, Drug polymer complex, Rapid disintegrating tablet, Wetting time, Taste evaluation.

INTRODUCTION

Recently, the clinical usefulness of tablets that are rapidly disintegrated by saliva (rapidly disintegrating tablet), has gained attention owing to their patient friendly characteristics [1]. They have proved to be ideal for geriatric and paediatric population, people suffering from dysphagia, clinical conditions where water intake is limited, situations where water is not available and for drugs undergoing high first pass metabolism [2]. The Rapid disintegrating tablet (RDT) has remarkable disintegration properties; without water, it is rapidly disintegrated in the mouth within only a few seconds. When the RDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration [3]. RDTs are useful in patients such as pediatric, geriatric, bedridden, or developmentally disabled [4, 5], who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style [6-8].

Taste making is an important step in the formulation of RDT of a bitter taste drug. Various approaches for taste making includes addition of flavors, chemical modification like prodrug preparation and restricting dissolution in saliva by coating or complexation. Douroumis DD et al. [9] prepared oral disintegrating tablets of cetirizine HCl which was previously coated with methacrylate polymer using fluidized bed coater to mask its bitter taste. By adding super-disintegrant, Shishu et. al. [10] successfully formulated fast disintegrating tablets of taste masked ornidazole microspheres

Venlafaxine HCl (VFX) is an intensely bitter drug used in psychologically uncompromised patient. It is also used in the treatment of chemotherapy-induced neuropathic pain and painful diabetic neuropathy [11-13]. It is well recognized that chemotherapy-induced neuropathic pain sometimes may be severe and disabling, compromise quality of life, and may cause further compliance problems in cancer treatment [14]. For the mentally retarded, uncompromised patient, administration of conventional tablets with water three times a day is difficult while in case of diabetic or chemotherapy-induced neuropathic pain rapid onset of action is desired. However, the problem of bitter taste of the drug is often encountered due to dissolution of the active ingredient in the mouth. Thus, in the present investigation an attempt has been made to improve patient compliance by formulating taste masked RDTs of VFX.

MATERIALS AND METHODS

Materials

Venlafaxine HCL (Batch No.62704003) was a gift from Ivax India Limited., Bombay, India. Aminoalkylmethacrylate copolymer (Eudragit EPO) was generously gifted by Degussa India Private Ltd., Mumbai, India. Microcrystalline Cellulose (MCC) (Ceolus KG 802, Asahi Kasei Chemicals Corporation, Tokyo, Japan) **and** spray-dried mannitol (Parteck M 200, Merck, Darmstadt, Germany) were used as diluent. The superdisintegrants were crospovidone (Polyplasdone XL-10, ISP Technologies, Inc, Calvert City, KY), croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Wallingstown,Ireland) and sodium starch glycolate (Primojel, DMV International, Belle Mead, NJ). All other chemicals used in the study were of analytical grade.

Determination of threshold bitterness concentration of the drug

Ten healthy human volunteers were chosen for the study, from whom informed consent was first obtained. All human volunteers held 10 ml of aqueous solution of VFX having concentration from 0 to 340 µg/ml in their mouth for 10 sec. and the concentration which induced bitterness was noted. Immediately after each test, volunteers rinsed their mouths with 50 ml of distilled water. (15, 16)

Preparation of drug-polymer complex (DPC)

VFX and Eudragit EPO complex was prepared using the precipitation method. Saturated solutions of VFX and Eudragit EPO were prepared in absolute ethanol in various ratios (Table 1). Solutions were then injected into NaOH solution with pH11 with constant stirring at 500 rpm for 5 min. The foamy matrix obtained on the top of the solution was separated, dried at room temperature for 24 h under vacuum and then pulverized in order to obtain a fine powder. These powdered complexes were stored in a tightly closed container for further studies. The optimized ratio was selected on the basis of drug release in simulated salivary fluid (SSF) pH 6.2 i.e*. in vitro* taste evaluations

Characterization of DPCs

Drug Content

Hundred milligrams of complex was dissolved in 500ml of simulated gastric fluid (SGF) using magnetic stirrer at 500 rpm for 1 h. An aliquot of 1 ml sample was withdrawn, suitably diluted and analyzed spectrophotometrically (Shimadzu-2401 PC, Japan) for drug content at 225 nm.

Molecular Properties of Drug on Complexation

The X-ray powder diffractograms of the DPC (1:3), VFX, Eudragit EPO, and physical mixture of VFX and Eudragit EPO (1:3) were recorded using Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Saint Jurie, Clubac, Canada). Samples were irradiated with monocrotized Cu Kα radiation (1.314A^0), at a speed of 2θmin^{-1} from 10° to 60° (2θ) under the voltage and current of 40Kv and 30Kv respectively.

IR spectra of DPC (1:3), VFX, Eudragit EPO and physical mixture of VFX and Eudragit EPO (1:3) were obtained by KBr disc method using Fourier-transform infrared (FTIR) spectroscopy (8400 S, Shimadzu Asia Pacific Pvt. Ltd., Singapore) in the range of 4000 to 500 cm^{-1}.

***In vitro* taste evaluation of drug complexes in SSF**

For the *in vitro* taste evaluation drug release was tested in SSF of pH 6.2 for an approximate estimation of drug release in the human saliva. DPC equivalent to 25 mg VFX was added to 10 ml of SSF in a volumetric flask and shaken for 60 sec on a mechanical shaker. The amount of drug released was analyzed spectrophotometrically at 225 nm [17].

Formulations of RDTs

Before formulation of tablets, the best superdisintegrants CP, CCS and SSG were screened at different concentration level ranging from 6 to 12 % for their disintegrant property. CP at 8 % w/w was found best among superdisintegrants tested, therefore it was added at the mentioned percentage in the preparation of different batches of RDTs. RDTs were prepared by mixing drug polymer complex 1:3 ratio with MCC/Mannitol in different concentration with CP as the disintegrants (Table 2). The powder blend was directly compressed using 8 mm flat-faced punches under compression force in the range of 500-1500 kgf.

Evaluation of Tablets

Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was kept in a culture dish (i.d. 5.5 cm) containing about 6 ml of purified water. A tablet having small amount of amaranth powder on the upper surface was placed on the tissue paper. Time required to develop red color on the upper surface of the tablet was recorded as a wetting time.

Same procedure was repeated for determining water absorption ratio without using amaranth. The wetted tablet was then weighed and water absorption ratio, R, was determined according to the following equation [16],

$$R = \left\{ \left(W_a - W_b \right) / W_b \right\} \times 100 \qquad (1)$$

Where, W_b and Wa are the weights of tablet before and after study.

Prepared tablets were also evaluated for hardness, tensile strength, friability, weight variation, and drug content (Table 3).

***In Vitro* Disintegration Study**

The tablet was dropped in 5 ml of SSF in test tube and time required for disintegration of tablet was measured (18).

***In Vivo* Disintegration Time and Sensory Evaluation of Roughness**

Study was performed with six healthy human volunteers, from whom informed consent was first obtained. After the mouth was rinsed with purified water, one tablet was held in the mouth and time required for complete disintegration of tablet was recorded. The same disintegrated material was held in the mouth for another 60sec. and then spat out immediately. Mouth was then rinsed with water without swallowing the disintegrated material and finally, the roughness levels were recorded on numerical scale ranging from 0 to 3 where 0, 1, 2 and 3 indicate no, slight, moderate and high roughness respectively [19].

Taste Evaluation

Taste evaluation was done using time intensity method for DPC and RDT. For this study a panel of eleven healthy human volunteers, from whom informed consent was first obtained were chosen. DPC equivalent to 25 mg VFX was held in the mouth for 10 sec and then spat out and for RDT, one tablet (containing 25 mg of VFX) was held in the mouth until complete disintegration. Bitterness was recorded immediately according to the bitterness intensity scale from 0 to 3. 0, 0.5, 1, 2 and 3 indicate no, threshold, slight, moderate and strong bitterness while '+'sign indicate good palatability. The readings were taken immediately and at several intervals over the period of 15min. After the study, mouth was rinsed well with water [20-22].

Dissolution study of tablets

In vitro dissolution of optimized tablets i.e. batch of DPC complex was carried out using USP type II (paddle) apparatus. Dissolution was carried out in 900 ml SGF without enzymes at 50 rpm and 37 ± 0.5°C. Aliquots (5 ml) were withdrawn and replaced by adding equal volume of fresh dissolution medium. Samples were suitably diluted and filtered and absorbance of filtered solution was determined at 225nm by using UV Spectrophotometer.

RESULTS

The minimum concentration among a range of dilutions of a substance at which the volunteer just starts feeling the bitter taste is known as threshold concentration. The threshold bitterness concentration of VFX as determined by a panel of 10 healthy human volunteers was found to be 330 µg/ml.

The mean percentage drug loading in DPC was found in the range of 97.88 ± 0.43 % to 99.23 ± 0.27 % (Table 1). Study on the *in-vitro* taste evaluation of DPC suggests that DPC of ratio 1:3 showed 1.35 ± 30% drug release with concentration of drug 13.5 µg/ml (less than threshold concentration). DPC with ratio 1:3.5 and 1:4 released 1.3% of drug which is not significantly ($p > 0.05$) less than that produced by the ratio 1:3. Hence, the ratio 1:3 was selected as optimized DPC ratio for the preparation of RDTs.

Table 1: Drug content and *In vitro* taste evaluation of drug complex

Drug-polymer complex Ratio	Drug content (% w/w)	% Drug released in SSF
1:1	98.45 ± 0.05	2.71 ± 0.21
1:2	98.74 ± 0.33	2.01 ± 0.27
1:2.5	99.21 ± 0.64	1.67 ± 0.19
1:3	98.93 ± 0.52	1.35 ± 0.30
1:3.5	97.88 ± 0.43	1.3 ± 0.25
1:4	99.23 ± 0.27	1.3 ± 0.19

**Results are mean of three observations ± standard deviation*

Table 2: Composition of RDT

Batches Ingredients (mg)	F1	F2	F3	F4	F5
DPC	104.16	104.16	104.16	104.16	104.16
MCC	73.84		49.22	36.92	24.62
Mannitol		73.84	24.62	36.92	49.22
CP	16	16	16	16	16
Sorbitol	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2

Formula for one tablet is shown in the table. Each tablet contain 25mg of VFX

Table 3: Evaluation of Tablets

Parameters	Formulations				
	F1	F2	F3	F4	F5
%Friability	0.25 ± 0.22	0.21 ± 0.10	0.18 ± 0.09	0.16 ± 0.23	0.26 ± 0.24
Content Uniformity (%w/w)	99.99 ± 0.46	100.03 ± 0.32	99.45 ± 0.34	100.15 ± 0.36	99.92 ± 0.41
Wetting Time (sec)	14.22 ± 0.18	19.35 ± 0.29	17.78 ± 0.16	14.78 ± 0.21	19.57 ± 0.23
Hardness	2.7 ± 0.31	2.9 ± 0.34	3 ± 0.04	2.8 ± 0.30	3 ± 0.18
Water Absorption Ratio	85.43	86.22	84.77	86.49	85.43
In Vitro disintegration time (sec)	20.92	25.3	33.8	20.16	30.43
In Vivo disintegration time (sec)	22	27	34	21	31

**Results are mean of three observations ± standard deviation*

Table 4. Comparative Taste Evaluation

Form of VFX	Degree of bitterness after time					
	10sec	1min	2min	5min	10min	15min
Pure drug	3	3	3	3	3	3
Drug-polymer complex	0	0.08	0.15	0.12	0	0
Unflavored tablet of DPC	0	0.02	0.19	0.01	0	0

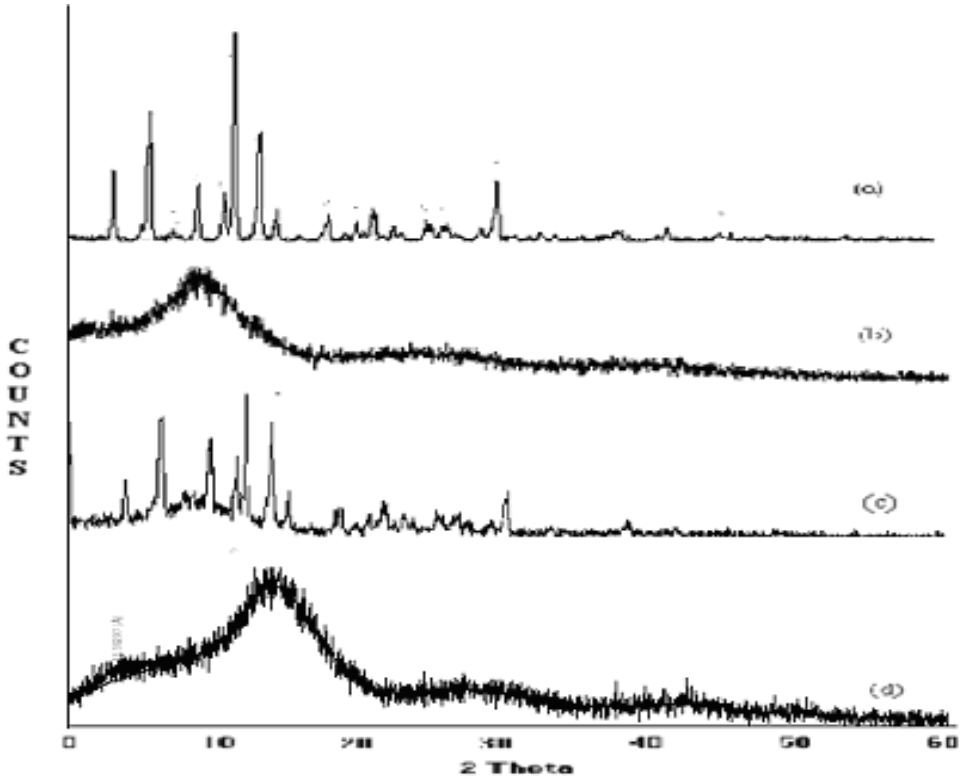


Figure 1. X-RD spectra of (a) VFXL (b) Eudragit EP0 (c) Physical mixture (d) DPC

The X-ray diffraction pattern of VFX exhibit sharp, highly intense and less diffuse peaks indicating the crystalline nature of drug. The X-ray diffraction pattern of physical mixture of VFX and Eudragit EPO was simply a superimposition of each component with peaks of both VFC and Eudragit EPO, however with lower intensity. DPC showed the complete disappearance of crystalline peak of drug situated between 10^0 and 40^0 (2θ) (Figure 1). The FTIR spectrum of the physical mixture of drug and polymer showed no significant shifts or reduction in intensity of peaks of VFX. However, DPC showed some significant differences in the characteristics peaks of drugs, showing modification of drug environment. The FTIR spectra of drug showed peak at 3350.12cm^{-1}, which was due to NH stretching supported by presence of sharp band at 1514.02cm^{-1}. Diminution and shifting of this peak from 3350.12cm^{-1} to 4000^{-1} was observed in DPC (Figure 2).

Properties like hardness, weight variation, content of tablets of all batches were found within acceptable limits (Table 3). Tablets of batch F4 containing spray dried mannitol and MCC in the ratio 1:1 and 8 % w/w CP showed minimum disintegration time (20.16 and 21sec) *in vitro* and *in vivo* respectively (Table 3) . The batch F5 containing higher amount of spray-dried mannitol showed increased wetting and disintegration time. All the human volunteers experienced bitter taste (score 3) up to 15 mins with pure drug, but with drug polymer complex degree of bitterness was from 0.08 to 0.12 (which was less than threshold score) (Table 4). Sensory evaluation of optimized tablet showed a good mouth feel with minimum grittiness. Time for 90% drug release of optimized tablet (formulation F4) was found before 60 sec in SGF suggesting rapid release of drug (Figure 3).

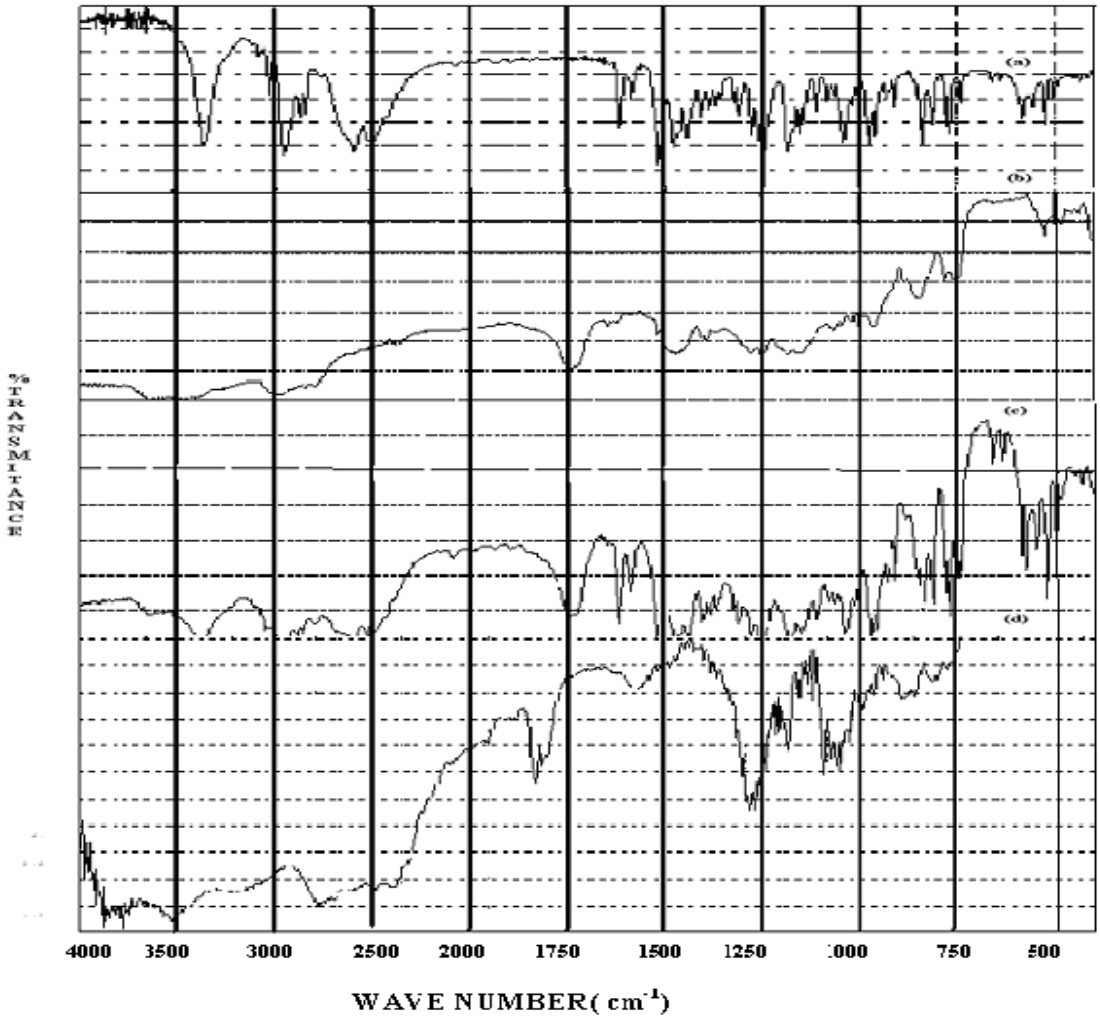
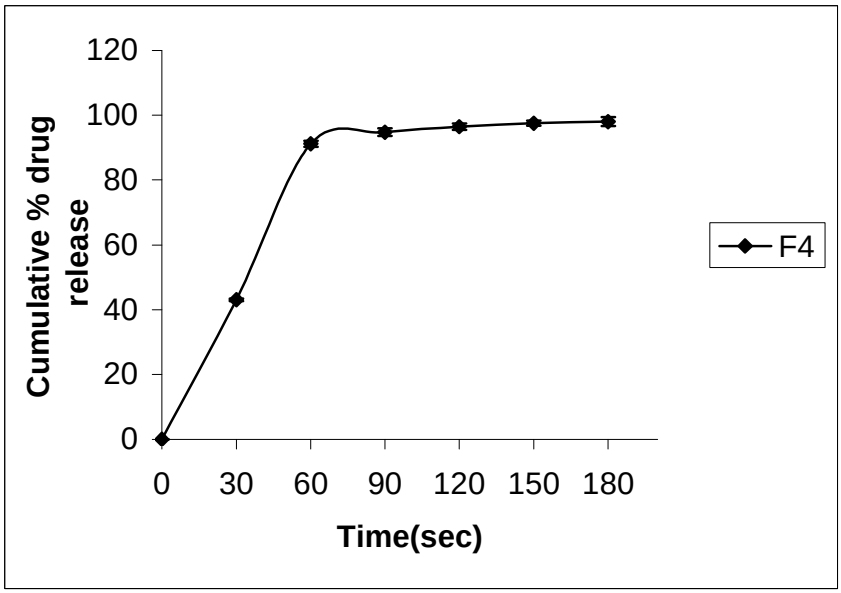


Figure 2. FTIR spectra of spectra of (a) VFX (b) Eudragit EP0 (c) Physical mixture (d) DPC

Figure 3: Dissolution profiles of optimized RDT (F4).



DISCUSSION

The DPC of ratio 1:3 showed drug release less than threshold concentration that gave bitter taste i.e. 330µg/ml. The findings of X-Ray diffraction suggest the presence of a new solid phase with a lower degree of crystallinity [23], which could be originated by the molecular interaction of the Eudragit EPO and VFX. The diminution and shifting of drug peak in DPC was observed due to blocking of groups by complex formation or may be overlapped by O-H stretching involved in hydrogen bonding. Thus hydrogen bond formation would have taken place between drug and polymer. Tablets containing CP more than 8 % w/w exhibited decrease in disintegration time due to formation of network of wetted particles of disintegrant that counteract the disintegration force. Higher concentration of mannitol in batch F6 might have increased disintegration and wetting time due to the increased viscosity of solution [24]. In vivo taste evaluation suggests that sufficient taste making has been achieved and that the bitter taste of the drug will not be perceived while the tablet is in the mouth after oral intake. In the sensory evaluation, all the volunteers experienced a good mouth feel of the VFX RDT with a minimum of grit.

CONCLUSION

By choosing optimimum DPC and by selecting a best superdisintegrant, it was possible to design RDT with taste masked VFX. Thus, this technology can be successfully used for formulating dosage form for psychologically uncompromised, paediatric, geriatric and bed ridden patients.

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