

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF APREPITANT BY USING NATURAL AND SYNTHETIC SUPERDISINTEGRANTS

RAJNI BALA^{1*}, SHAILESH SHARMA², IKGPTU³

¹Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, S. B. S. Nagarn, ²Department of Pharmaceutics, ASBASJSM COP, Bela, ³Inder Kumar Gujral Punjab Technical University, Jalandhar
Email: rajnibpharma@gmail.com

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ABSTRACT

Objective: The present study was aimed to formulate fast dissolving tablets (FDTs) of Aprepitant (APT) using natural and synthetic superdisintegrants with the desired onset of action, increased bioavailability by reducing the frequency of dosage and also reduce the first-pass metabolism of the drug.

Methods: In this research, the gum isolated from *cordia dichotoma* was investigated as super disintegrants in fast dissolving tablets (FDTs). The aprepitant tablets were prepared separately using *cordia dichotoma* (natural), sodium starch glycolate and croscarmellose sodium (synthetic) as superdisintegrants by direct compression method. The tablets were evaluated for various precompression and post-compression parameters.

Results: The optimized formulation (APT F3) of *cordia dichotoma* (8%) showed satisfactory physicochemical properties, minimum disintegration time (34 seconds) and highest dissolution rate (86.52%) in 10 min than the other synthetic superdisintegrants. Also, the pharmacokinetic study of the optimized formulation showed effective results as compared with marketed product of aprepitant.

Conclusion: The developed formulation can improve the onset of action as well as improve patient compliance.

Keywords: Aprepitant, Superdisintegrants, Fast dissolving tablet, Direct compression, Evaluation, *In vivo* studies

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INTRODUCTION

Nausea is an unpleasant sensory and emotional experience accompanied by an autonomic driven physiological change of paller and upper GI track hyper secretion [1]. Current oral formulation of aprepitant are indicated for administration of multiple doses, which was due to the half-life of approximately 9-13 h with a time to peak plasmas level of 4 h [2].

Approximately 40% of patients who receive chemotherapy have experienced with nausea and vomiting [3, 4]. Control of nausea and vomiting following chemotherapy and surgery has been improved in recent years due to the advancement of novel, effective, and better-tolerated antiemetic therapies [5-7]. Conventional oral drug delivery systems, including solutions, suspension, tablets and capsules are difficult to administer to patients with dysphagia. Swallowing problems can also be appear often in specific populations, including pediatric, elderly, nauseated patients and developmentally disabled patients. In addition to these difficulties convenience is also a notable concern associated with oral antiemetics like the patients taking tablet formulations require water to ease swallowing, which is not always available [8, 9]. Also, crushing tablets or removing contents from capsules may change the absorption of a drug. In addition to change in nontraditional drug delivery systems, oral delivery formulations have continued to develop to enhance the dissolution and absorption. Fast dissolving tablets (FDTs) have been designed to allow a solid dose to be rapidly dissolved in the oral cavity without the need for water [10-12].

Several approaches have been used to formulate FDTs like freeze-drying, tablet molding, sublimation, direct compression, spray drying etc. Out of these direct compression and lyophilization have become the most popular used techniques. The tablets prepared by lyophilization technique have very porous structures and hence allow fast disintegration of the tablets. However, high porosity leads to poor physical resistance, in addition to its cost-intensive production process. On the other hand the tablets produced by direct compression method can be hard and attain low friability. This method requires efficient disintegrants to enhance the breaking up of the tablets [12-14].

Hence, based on the rationale of the proposed research work, the aim of the present study was to develop and formulate fast dissolving tablet of aprepitant by direct compression method for the direct absorption of drug via transmucosal lining to the systemic circulation. The proposed formulation has the potential to improve disintegration time and possess sufficient mechanical strength to produce rapid onset of action and patient compliance.

MATERIALS AND METHODS

Materials

Aprepitant was obtained from Hetero Labs Ltd, Baddi, India. *Cordia dichotoma* fruit was collected from northern region of Rajasthan, microcrystalline cellulose (SD Fine Chemicals), sodium starch glycolate, croscarmellose sodium (DFE Pharma) and all other chemicals were used of analytical grade without any further modification.

Methods

Isolation of gum from *cordia dichotoma* fruit

The whole plant of *Cordia dichotoma* (family Boragenaceae) was procured from northern region on Rajasthan's district Sri Ganganagar. It was shade dried and stored in a tight closed container. This variety was identified and authenticated by as *Cordia dichotoma* from National institute of science communication and information Resources (NISCAIR/ RHMD/Consult/1450/48).

It was taken as plant parts such as fruit have been reported for possessing super disintegrant activity. Plant material was washed, then macerated with water (1:2) and stirred for 3 h. The viscous solution was obtained by addition of 95% ethanol with continuous stirring and was filtered through the muslin cloth. Precipitation of the mucilage was carried out. The precipitated polysaccharide was dried in oven at 40-45 °C. The dried product was powdered and passed through sieve no 60. The product was kept in airtight containers. The isolated gum was investigated for physicochemical properties such as swelling index, solubility, pH and loss of drying and its powder flow properties [15-18].

Physicochemical characterization of the polysaccharide obtained from *cordia dichotoma* fruit

Swelling index (SI)

SI is defined as the determination of the amount of the liquid taken by the powder. The sample (1g) was filled into the 50 ml measuring cylinder. After placing the solid sample, it was tapped 10 times to obtain possibly the same packaging of bed. Phosphate buffer pH 6.8 (25 ml) was added by shaking every 10 min for 1 h [19]. The swollen mass was allowed to stand for 24 h. The SI was estimated as:

$$SI = 100 * (Ht - Hi)/Hi$$

Where Hi = initial height of material before hydration; Ht = Height of hydrated material.

Determination of pH

pH was investigated by taking 1% w/v dispersion of *cordia dichotoma* using digital pH meter. The pH was noted after immersing the electrode of the pH meter in contact with the dispersion [20].

Loss of drying (LOD)

The presence of moisture in the powder may affect the stability of the dosage form. Therefore loss of drying was determined by loss of drying technique. The sample was weighed and dried in oven for 2 h. The sample was allowed to cool in desiccator and weighed again. The percentage weight loss was determined by using the formula.

$$\% \text{ LOD} = 100 * \frac{W1 - W2}{W1}$$

Where W1= initial weight of powder; W2= final weight of powder

Drug excipient interaction study

Fourier transform infrared spectroscopy (FTIR)

The physical mixtures of aprepitant and *cordia dichotoma* were used to check the physicochemical compatibility by FTIR absorption spectra. The graph was recorded in the range of 4000–400 cm⁻¹ by KBr pellet method using FTIR spectrophotometer (Spectrum GX, Perkin-Elmer, USA).

Differential scanning calorimetry (DSC)

The thermal properties of the pure drug and polysaccharide with their mixtures were assessed using differential scanning calorimeter using DSC-PYRIS-1 (Perkin-Elmer, USA). The analysis was achieved with heating at 50–48 °C and a rate of 10 °C min⁻¹ in an inert nitrogen atmosphere.

Preparation of fast dissolving tablets of aprepitant

Direct compression method was used to prepare fast dissolving tablets using natural and synthetic superdisintegrants (table 1). The raw material was passed through sieve no 100 prior to mixing. Lubricants were added in this mixture at last. The blend was then converted into the tablet by using a single punch machine (table 1). The prepared tablets were evaluated for pre and post parameters. The evaluated tablets were compared with the tablets prepared by synthetic superdisintegrants.

Precompression parameters of the powder blend

The physical mixture of the blend was evaluated for its micrometric properties (bulk density and tapped density) and flow properties (angle of repose, compressibility index and Hausner's ratio) [21].

Table 1 Composition of fast dissolving tablets

Ingredients (mg)	APT F1	APT F2	APT F3	APT F4	APT F5	APT F6	APT F7	APT F8	APT F9
Aprepitant	40	40	40	40	40	40	40	40	40
<i>Cordia dichotoma</i>	4	6	8	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	4	6	8	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	4	6	8
Avicel PH102	87	85	83	87	85	83	87	85	83
Mannitol	60	60	60	60	60	60	60	60	60
Sodium Saccharine	1	1	1	1	1	1	1	1	1
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4

Angle of repose

The angle of repose was determined using funnel method. The funnel was mounted at fixed height on the stand. A fixed weight quantity of blend was allowed to pour through the funnel. The height and diameter of the pile were noted. The angle of repose was calculated by

$$\tan\theta = \left(\frac{\text{height}}{\text{base}}\right)$$

Hausner ratio and compressibility index

The Hausner ratio and compressibility index involves the measuring of bulk volume (Ho) and tapped volume (Hf). The calculations are done as:

$$\text{Compressibility index} = 100 * (Ho - Hf)/Ho$$

$$\text{Hausner ratio} = (Ho/Hf)$$

Evaluation of post compression parameters of FDTS

Weight variation

Weight variation test was performed on twenty tablets as per USP, calculating the individual weight and average weight and then comparing the individual tablet weights to the average. The average weight of one tablet was noted [22].

Tablet crushing strength

Tablet crushing strength of each formulation was noted using Monsanto Hardness Tester. It was determined to check the

condition of tablets during storage, shipping and handling before usage.

Friability (% F)

Roche friabilator was used to determine the friability of the tablets. Prewedged tablets were placed in the friabilator at a height of 6 inch and subjected to revolve at 25 rpm for 4 min [23]. Tablets were reweighed after removing fines. The friability (F %) was calculated by the formula.

$$\%F = 1 - \frac{\text{loss in final weight}}{\text{initial weight}} * 100$$

Disintegration time (DT)

US FDA described that the disintegration of the tablet is achieved in the oral cavity. Phosphate buffer pH 6.8 (6 ml) was taken in a 25 ml beaker as amount of saliva in the oral cavity is limited (approx. 6 ml). The temperature was maintained at 37±2 °C [24, 25]. A tablet was placed into the beaker and time required for complete disintegration of the tablet was noted.

Wetting time (WT)

A piece of circular tissue paper was kept in a petri dish containing 6 ml of phosphate buffer (pH 6.8) containing amaranth dye. The tablet was placed on the surface of tissue paper and the time to reach the solution at the upper surface of the tissue paper was determined as wetting time of tablet.

Uniformity of content

Ten tablets were crushed to the powder and powder equivalent to 40 mg of drug was dissolved in the phosphate buffer pH 6.8. This solution was filtered and injected into the HPLC. The drug content was determined by an average of three random samplings of all batches [26].

In vitro drug release studies

30 ml phosphate buffer (pH 6.8) with 1% w/v SLS in a beaker (37 ± 0.5 °C) was used to determine the dissolution profile of tablets. Whole assembly was then placed on a shaker. 1.0 ml sample aliquot was withdrawn and replaced with the same fresh media at different time intervals. Samples were filtered and diluted with phosphate buffer (pH 6.8). The filtrate was analyzed by using HPLC. The *in vitro* release data obtained was exposed to zero-order kinetics to understand the release mechanism [27, 28].

In vivo study design study

New Zealand healthy male rabbits (weighing 2.6-3.1 kg) were selected for the study. The experimental animals were procured from MMIMSR MM University, Mullana. All animal experiments were carried out after approval of the protocol by the Institutional Animal Ethical Care (IAEC) committee (RIP/IAEC/2016-2017/07) guidelines for the use and care of experimental animals. The procured rabbits were acclimated for 10 d in proper cages at air conditioned temperature having average feed intake around 40-50 g and free access to water.

For *in vivo* study all rabbits were fasted for 12 h before administration of formulations and then divided into two groups. One group received apreptant loaded FDT whereas the other group received the marketed formulations (Apreptant equivalent to 1 mg/kg). The FDT was carefully placed on the rabbit tongue with body restraint device in which the animal's head was exposed and lifted apart the gums. The mouth of animal was wetted with small amount of water [29, 30] and tablet was placed in the mouth. A gentle strain was also applied to restrict the mouth in order to confirm the complete breakdown of the tablet [31]. About 0.5 ml blood samples were withdrawn from the peripheral vein of each rabbit at the interval of 0,1,2,3,4,5,7,9,12,24 h for the determination of pharmacokinetic study.

Preparation of plasma samples for HPLC analysis

The blood sample (0.5 ml) containing disodium EDTA was withdrawn in the centrifugation tube. The sample was centrifuged at 5000 for 10 min. The plasma proteins were precipitated with the addition of acetonitrile [32-34]. The supernatant was transferred to a test tube and evaporated to the dryness. The residue was reconstituted with acetonitrile and dilute phosphoric acid to determine apreptant in blood sample by HPLC method. Pharmacokinetic parameters was analyzed in this study

RESULTS

The dried polysaccharide powder isolated from *cordia dichotoma* was brown in color. Further, the polysaccharide was evaluated for physicochemical characterization as shown in table 2.

Table 2: Physicochemical properties of *Cordia dichotoma*

S. No.	Parameters	Results
1	State	Solid
2	Color	Brown
3	pH	6.9-7.3
4	Solubility	Soluble in hot water, insoluble in organic solvent like methanol, ethanol, chloroform.
5	Swelling index	97%
6	Loss of drying	8.34%

The polysaccharide is freely soluble in hot water and forms viscous solution but practically insoluble in organic solvent. The pH of 1% w/v solution of polysaccharide was found to be near neutral. Loss on drying was observed within acceptable limits. The FTIR spectra obtained for apreptant showed strong absorption peak at 1704 cm^{-1} which specified C=O stretching, C-H stretching over the range

$1500\text{--}1600\text{ cm}^{-1}$, C-F stretching at 1132 cm^{-1} . The FTIR of *cordia dichotoma* sample presented characteristic peak at 3449 cm^{-1} which indicated C=O stretching vibration peak. The strong peak at 2924 cm^{-1} specified C-H bond. The peak at 1622 cm^{-1} indicated presence of saponins glycosidic bond and the peak at 1407 cm^{-1} showed a O-H bond indicating the presence of flavonoids.

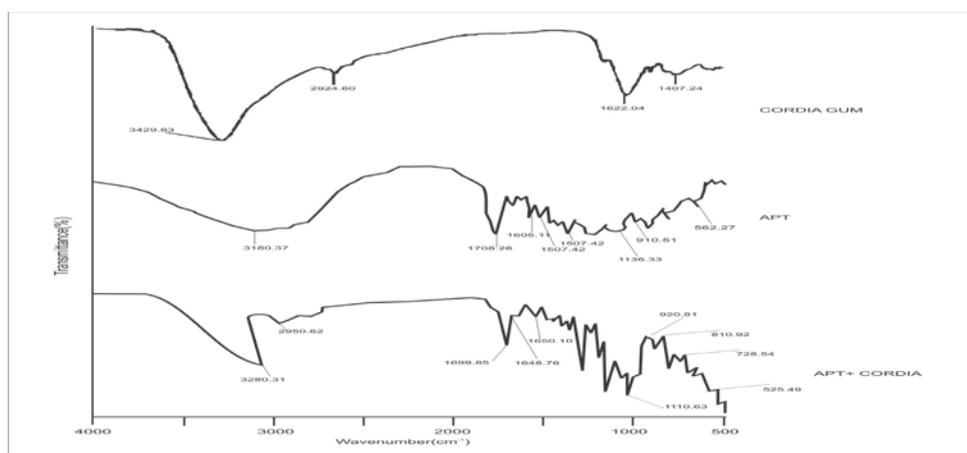


Fig. 1: Comparison of FT-IR of *cordia dichotoma*, apreptant (APT) and mixture of both

A DSC thermogram of pure polysaccharide showed endothermic peak at 148 °C corresponding to its melting point and pure apreptant displayed

endothermic peak at 248.2 °C. The transition temperature for the physical mixture was decreased in the melting point by approx 10-15 °C.

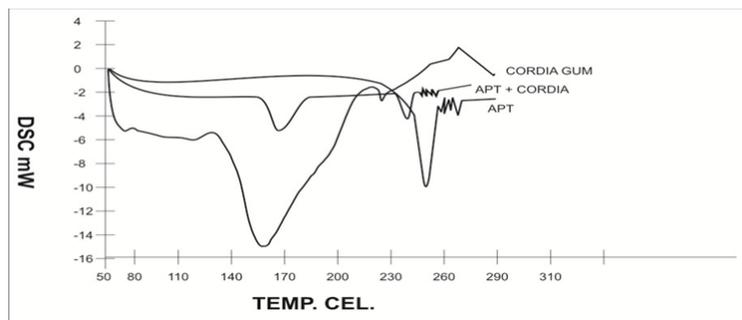


Fig. 2: Comparison of DSC of *cordia dichotoma*, aprepitant (APT) and mixture of both

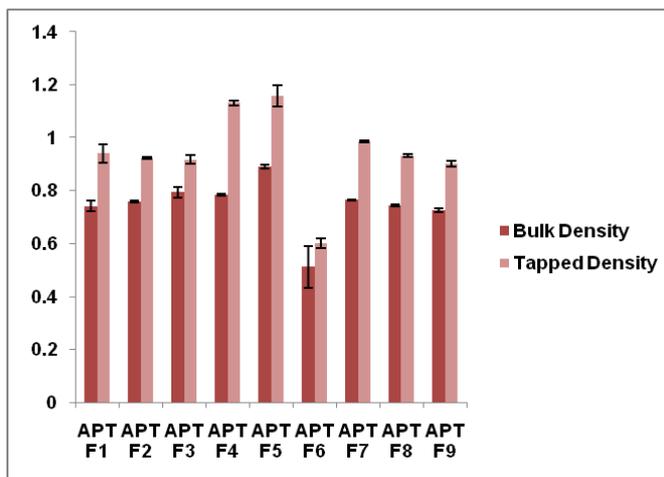


Fig. 3: Graphical presentation of bulk density and tapped density (mean±SD, n = 3)

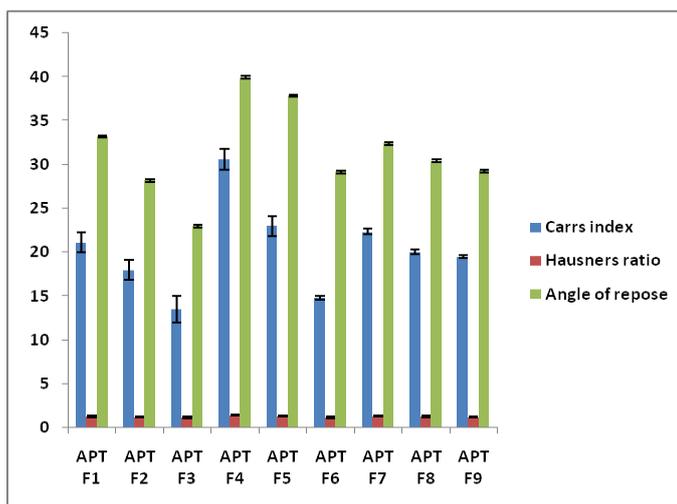


Fig. 4: Graphical presentation of flow properties of all batches (mean±SD, n = 3)

The results from the pre-compression parameters of powder blend revealed good flow properties in well acceptable limits as shown in fig. 3 and 4.

Aprepitant fast dissolving tablets were prepared by direct compression method using natural and synthetic superdisintegrants in optimized concentration and evaluated according to the post-compression parameters.

The average weight of FDTs batches were found in the range of 198.7-202.4 mg signifying weight variation is uniform. The mean hardness values for all the batches were found to be 2.6-3.8 kg/cm³

indicating hardness of the tablet. The %age friability was found to be in the range of 0.45 to 0.72% revealing physical integrity of the tablet.

All the batches of FDTs contained 98.56 to 101.87% of drug content which indicated the uniformly distribution of the drug. The *in vitro* drug release results indicated that the speed of disintegration depends upon swelling pressure, surface area and hydration capacity. On increasing the concentration of *cordia dichotoma* (natural super disintegrants), faster the wetting and disintegration of tablets which may be due to rapid absorbing nature including swelling and capillary action of polysaccharide.

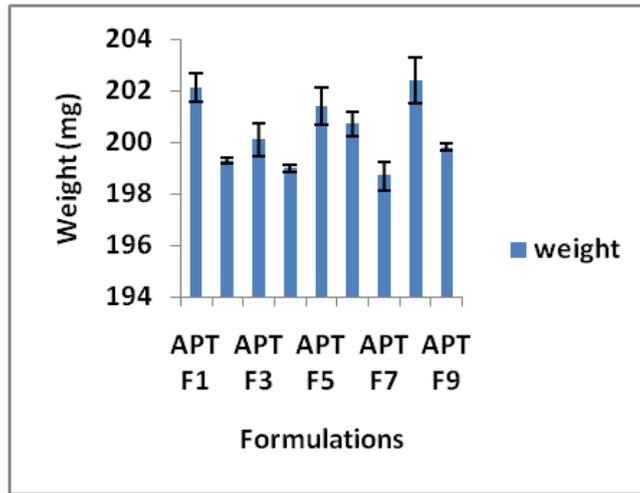


Fig. 5: Weight Variation of all batches (mean±SD, n = 3)

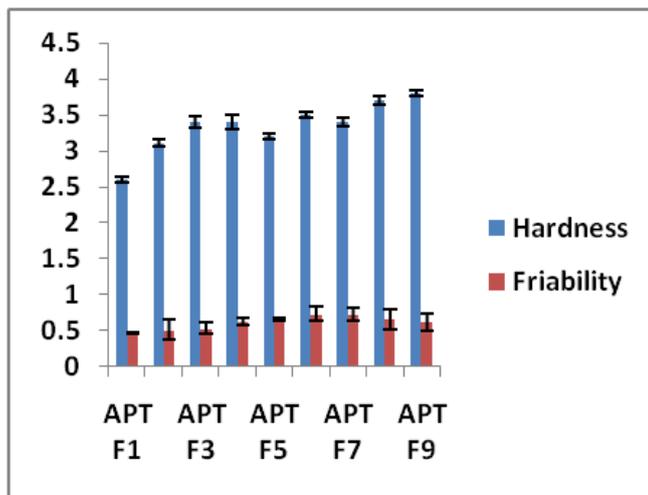


Fig. 6: Graphical presentation of hardness and friability of all batches (mean±SD, n = 3)

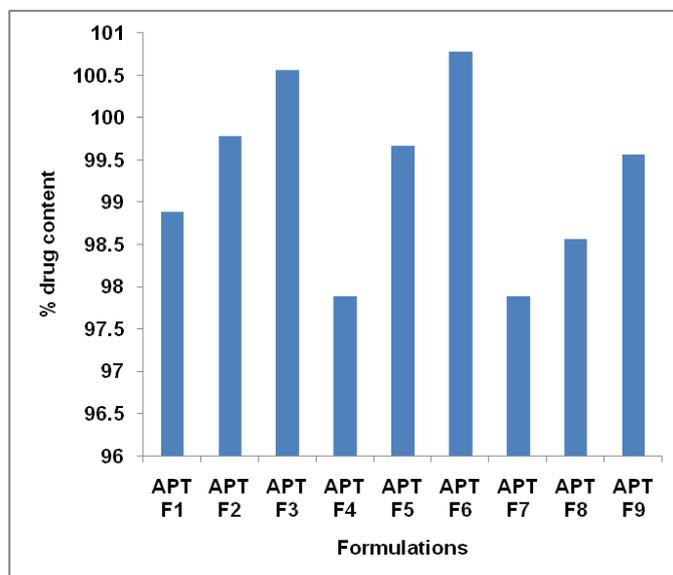


Fig. 7: Drug content of all batches (APT F1-APT F9)

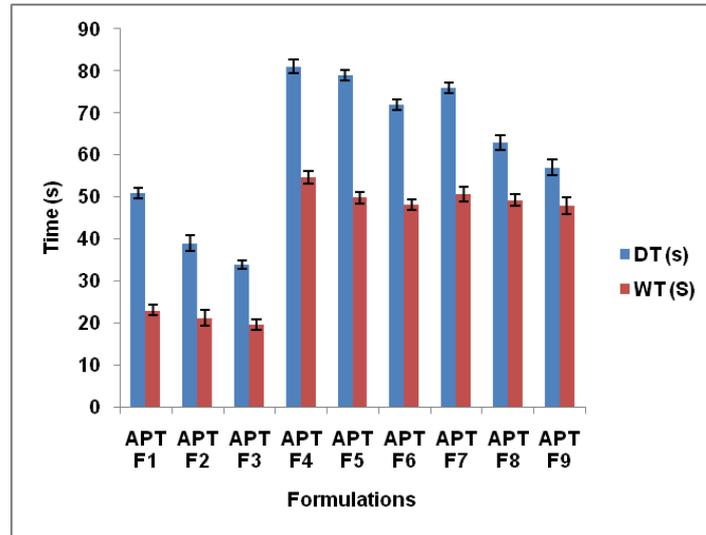


Fig. 8: Graphical presentation of DT and WT of all batches (mean±SD, n = 3)

On the contrary, when the concentration of SSG and CCS (synthetic superdisintegrants) was increased, this had a negative effect on the disintegration of the tablets. It may be due to the gel layer formation, which may hinder the penetration of medium and hence disintegration of the tablet [35, 36].

The plasma concentration-time profile was obtained for animal pharmacokinetic study (fig. 10). Pharmacokinetic parameters including AUC, AUMC, plasma concentration (C_{max}), time to reach C_{max} (T_{max}) and mean residence time (MRT) were determined using Winnonlin Software.

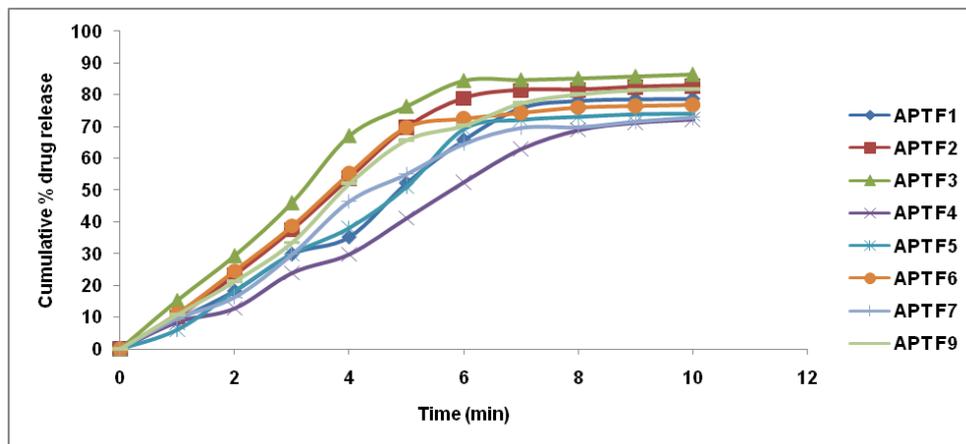


Fig. 9: Comparative study of percentage drug release of tablet formulations

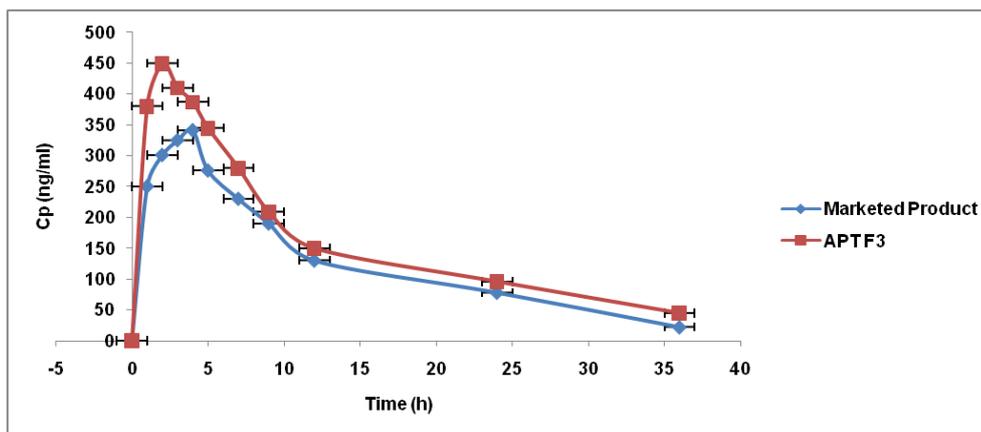


Fig. 10: The pharmacokinetic profile of optimized fast dissolving tablet and marketed product (mean±SD, n = 3)

The average peak plasma-concentration time profile obtained from APT F3 signifying an increase in AUC as compared with marketed product. Similarly, there was increase in rate of absorption (Cmax)

for APT F3 (table 3), representing that aprepitant was more promptly absorbed in the fast dissolving tablet and attaining higher plasma concentration in short intervals than marketed formulation.

Table 3: Pharmacokinetic parameters

PK parameters	APT F3	Marketed product
AUC(ng. h/ml)	5774±278.42	4609±234.78
Tmax (h)	2.00±0.45	4.00±0.47
Cmax (ng/ml)	450±25.45	341±17.43
AUMC (ng. h ² /ml)	66136±2341.88	51672±1987.54
MRT (h)	11.4541±0.32	11.2111±0.37

*All values are expressed as mean±SD, n = 3 (for standard deviation), the higher values of pharmacokinetic parameters indicated the improvement in bioavailability of the drug by formulating them into fast-dissolving tablets.

DISCUSSION

The polysaccharide obtained from *cordia dichotoma* was brown, freely flowing powder. The main concern was to select the suitable concentration of super disintegrants to develop a successful fast dissolving tablet. It was studied for powder flow properties, swelling index, pH and loss of drying [37]. The results were found within the acceptable limits of the above properties as shown in table 2. The FTIR-ATR of the aprepitant loaded super disintegrants indicated the characteristic peaks which indicate purity of drug and polymer; hence there was no interaction between drug and other excipients as shown in fig. 1. DSC also indicated that there was no change in aprepitant in the fast dissolving tablet as shown in fig. 2. Due to its good swelling properties, an attempt was made to prepare the fast dissolving tablet with polysaccharide to explore the potential as super disintegrants. The micrometric properties of polysaccharide indicated good packing and flow properties as shown in fig. 3 and 4.

The fast dissolving tablet of aprepitant was prepared by direct compression method using natural and synthetic superdisintegrants in the same concentration. The prepared tablets were evaluated for its post-compression properties. The weight variation was complied with pharmacopoeial limit as shown in fig. 5. The friability and hardness study indicated the good physical and mechanical strength of the tablet (fig. 6). The percent drug content of tablets was within acceptable range indicated uniformity of content in all formulations as shown in fig. 7.

The tablets prepared by polysaccharide acquired less wetting time and *in vitro* disintegration time. It could be due to higher swelling properties of polysaccharide which increased the water absorption capacity and thus tablets disintegrated quickly as compared to synthetic properties as shown in fig 8. A rapid increase in drug penetration increased the drug porosity and thus, improved the dissolution of the drug. In case of synthetic superdisintegrants, dissolution occurred slowly because of formation of viscous gel layer [38] Thus, it was concluded from *in vitro* drug release study that APT F3 was selected as the best formulation as shown in fig. 9. The different pharmacokinetic parameters (AUC, AUMC, Tmax, Cmax and MRT) were estimated from the data obtained. The results suggested enhancement in AUC and AUMC when aprepitant was administered in fast dissolving tablet. Moreover, there was no significant difference in Tmax and MRT suggesting that different forms of APT in dosage did not influence mean residence time and maximum time to attain the maximum concentration of aprepitant [39].

Thus APT F3 indicated higher rate dissolution as compared to synthetic superdisintegrants. The optimized fast dissolving tablet showed a 34 sec disintegration time with sufficient wetting time and 86.52% drug release. Further, a significant difference in AUC and AUMC of the formulation indicated improvement in the oral bioavailability of aprepitant.

CONCLUSION

The study was aimed to formulate fast dissolving tablets of anti-emetic drug aprepitant to achieve faster drug release to control in nausea and vomiting. An increased concentration of polysaccharide leads to significant effect on the disintegration as well as dissolution

rate. Improvement in pharmacokinetic parameters (AUC, Cmax, Tmax, AUMC and MRT) and in bioavailability offer advantages in terms of the quick onset of action and patient compliance as compared with marketed product. Hence, it can be concluded that the *cordia dichotoma* polysaccharide acts as good super disintegrants as compared to synthetic agents.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest

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