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CINNARIZINE ORODISPERSIBLE TABLETS: A CHITOSAN BASED FAST MOUTH DISSOLVING TECHNOLOGY

Mitesh Nagar[1] * and A. V. Yadav[2]

[1] Department of Pharmaceutics, Govt. College of Pharmacy, Karad, Maharashtra, India.
[2] Department of Pharmaceutics, Goa College of Pharmacy, Panji, Goa, India.
***Postal address: Department of Pharmaceutics, Govt. College of Pharmacy, Karad, Vidyanagar, Karad, Dist. Satara (MS), INDIA,PIN – 415 124**

Corres.author: miteshnagar@yahoo.com
Fax No.: +91 2164 271196, Phone No.: +91 99705 86305

ABSTRACT: In recent days the use of fast mouth dissolving tablets are well accepted by elderly, children and the patients having trouble in swallowing and even by the travelling patients who find it convenient to ingest. Cinnarizine is a piperazine derivative and is widely prescribed for the treatment of vestibular disorders and motion sickness. To enhance the anti-emetic and anti-migraine properties of Cinnarizine it is desirable to develop its fast acting dosage form hence a fast mouth dissolving tablet of Cinnarizine is always a better choice. Chitosan is the best known natural polysaccharide used for its versatile applications in pharmaceutical industry. Superdisintegrant property of chitosan has been utilized to develop a fast mouth dissolving tablet by utilizing a novel method of treatment which can replace any other superdisintegrant. The properties of the rapidly dispersible tablet, such as porosity, hardness, disintegration time, wetting time and dissolution time, were investigated accordingly and the formulation was optimized as per 3 level full factorial design and analysed for response surface methodology to decide the best formulation which further evaluated for in-vitro performances. Fast mouth dissolving or OroDispersible tablets (ODTs) of Cinnarizine with acceptable compression parameters and pleasant mouth feel could be prepared within the optimum region hence Cinnarizine OroDispersible tablets (CODT) can be prepared which upon administration disperse in mouth as soon as in contact with saliva and release the drug content immediately which can be absorbed directly through oral mucosa or can be swallowed without the aid of water hence provide faster and better therapeutic effects.
Keywords: Cinnarizine; OroDispersible tablets; Chitosan; Superdisintegrant

1. INTRODUCTION

Despite couple of disadvantages, the oral route of drug administration is the most common and convenient for patient use. Tablets and capsules have emerged as the most popular solid oral dosage forms used. Novel oral drug delivery systems that dissolve or disperse quickly in a few seconds after placement in the mouth without water can alleviate the problem of swallowing tablets. They enhance the potential for improved compliance in patients. OroDispersible systems are defined as systems that dissolve or disintegrate within seconds to a few minutes after placement in the mouth and do not require water to aid swallowing. A key attribute of these technologies is the fact that the tablets rapidly disintegrate, and the constituents partially dissolve in the mouth by the action of saliva which upon swallowing leads faster absorption also from pregastric sites such as the mouth, pharynx, and oesophagus as the saliva passes down into the stomach. In these cases, the bioavailability of drugs from these formulations might be greater compared to the conventional oral dosage forms.[1] Researchers have formulated ODT for various categories of drugs, which require rapid onset of peak plasma concentration to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic drugs and drugs for erectile dysfunctioning.[2]

The performance of an ODT depends on the technology used in its manufacture. The disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the

appropriate disintegrating agent and using highly water-soluble excipients in the formulation. ODT can be achieved by various techniques like direct compression, wet granulation, freeze-drying, tablet moulding, spray drying, sublimation, cotton candy process and mass-extrusion. Among the various marketed fast mouth disintegrating or dissolving technologies the most popular are WOWTAB, when placed in the mouth rapidly becomes soft by absorption of saliva and disintegrates or dissolves within 15 to 20 sec.,[3] Zydis dosage form is a freeze-dried when placed on the tongue, the tablet structure disintegrates, instantaneously releasing the drug in the mouth upon disintegrates in about 10 sec.,[4] OraSolv technology and commercialized various quick-dispersible products disintegrate within 60 sec. Combination of rapid-releasing microparticles with the effervescent disintegration agents provides effective taste masking of the drug in OraSolv.[5,6] Shearform technology comprises a mixture of saccharides and sugar alcohol processed in a way to provide uniform flow properties and physical integrity of the matrix.[7] The Shearform floss is blended with other ingredients and introduced in a dosage well, compressed at low pressure and cure shrinked at adequate conditions to produce a crystalline matrix which disintegrates in approx 10 sec.[8] Extra attention is required to be given to develop ODTs as there are certain tabletting parameters which need to be compromised to potentiate the desirable properties of ODT like fast and complete disintegration, uniform dispersion and good mouth feel which may lead to less tablet hardness, hampered friability and handling problems and less strength and high porosity may lead to shorten shelf life. There was no specification concerning the hardness and the friability of this kind of tablets. That is why we find certain ODTs or RDTs in the market that disintegrate in less than 1min or may be 30 sec. but are brittle and require specified peelable blister packaging and thus higher costs.[9] The aim of this study was to develop and characterise a novel chitosan based ODT which possess all the basic requirements of fast disintegrating tablets viz. sufficient mechanical strength, better taste, good mouth feel, rapid disintegration time of less than 1 min. and should form a good suspension with saliva which can be swallowed without water. As the production of CODT using a simple and economical method is highly desired, in the present research work we planned to develop a simple, economical and effective technology which yield the better product in terms of improved oral absorption, faster onset of action, minimized first-pass effect, improved oral bioavailability, improved compliance, contain necessarily the GRAS (Generally Regarded As Safe) excipients, using common process and conventional equipments and finally involving chitosan as the model excipient for its superdisintegrant properties and importantly possessing sufficient mechanical strengths to avoid sophisticated techniques involved in packaging and handling.

Chitosan is a natural polymer obtained by deacetylation of chitin which is the second most abundant polysaccharides in nature after cellulose. Being a bioadhesive polymer and having antibacterial activity, chitosan is being used in ophthalmic, nasal, oral, gastrointestinal, colon-specific, vaginal, and transdermal drug delivery systems and also includes its application as a mucosal-vaccine carrier.[10] Chitosan has received considerable attention as a possible pharmaceutical excipient in recent decades due to its good biocompatibility and low toxicity properties in both conventional excipient applications and in novel drug delivery applications. Along with general applications as diluent, disintegrant, binder, Preparation of hydrogels, viscosity increasing agent in solutions, wetting agent, and improvement of dissolution of poorly soluble drug substances, bioadhesive polymer, polymer for site-specific drug delivery, Absorption enhancer, biodegradable and polymer Carrier in relation to vaccine delivery or gene therapy are some novel use.[11] Superdisintegrants are the sole of dispersible or fast disintegrating tablet technology as they are water insoluble though hydrophilic materials, they produce extremely fast disintegration and used in very less concentration (generally 2 - 5%). In general use crosscarmellose sodium, sodium starch glycolate and crospovidone are the few superdisintegrants used frequently for such applications. Chitosan though has been reported to be used for its disintegration properties in conventional dosage forms but its novel use as a superdisintegrant has been thought for the first time and confirmed in the present research work to establish its application as an effective superdisintegrant. The major objective of this research work was to evaluate and optimize the superdisintegrant properties of chitosan hence it was intended to use the minimum possible quantity of the chitosan in the system which can produce the optimum superdisintegrant property. Cinnarizine is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by menierre's disease and other vestibular disorders and for the prevention and treatment of motion sickness. It is also used in the management of various peripheral and cerebral vascular disorders.[12] Cinnarizine is absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. It undergoes metabolism and has a half-life of 3 to 6 hours. The usual dose of Cinnarizine for vertigo and vestibular disorders is 30 mg three times daily by mouth. For motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. For both the indications Cinnarizine can be given to children aged 5 to 12 years in half the adult dose. A dose of 75 mg once or twice daily has been given for vertigo and vestibular disorders. The available marketed dose of Cinnarizine is 25 mg and 75 mg conventional tablets which can be given according to the convenience.[12,13] A better delivery system for Cinnarizine is always desirable which can provide the prophylactic as well as fast symptomatic relief from

various disorders like migraine, emesis and vertigo so the CODT can be the dosage form of the choice to be produced and marketed hence to prepare a CODT for better compliance, easy to formulate, suitable to market and possess industrial applicability. Hence to formulate an ODT by using chitosan as superdisintegrant without compromised tablet properties and which can be taken without water to offer high Patient compliance are the objectives of this study.

2. MATERIALS AND METHODS

Cinnarizine (gift sample from Geno pharma, India), was taken as model drug for the study to justify the need of an ODT. Microcrystalline cellulose Avicel PH 102 (Provided by Sanofi Aventis India Ltd., Goa) used as bulking agent because of its insoluble nature, good potential for wet granulation technology and good compressibility, Chitosan 652 with degree of deacetylation 90% (Daksh ltd., India) was used being highly deacetylated and having very less average particle size of 75 microns, Acetic Acid Glacial (AR grade, Loba Chemie) was used as the solubilising agent in preparation of chitosan solution, Citric Acid used as taste modifier, Aspartame (Quarrechin, France) as sweetener, Menthol as flavouring agent, Colloidal silicon dioxide (Aerosil 200, Degussa, Germany) and Magnesium stearate were used as glidant and lubricant respectively. All other solvents and reagents used in were of analytical grades.

2.1 Preparation of Fast disintegrating granules (FDG):

Chitosan solution was used as the granulating liquid which was prepared by dissolving chitosan in acetic acid solution the ratio of chitosan to Acetic acid was taken as (60:40) by weight. The chitosan solution was prepared by first adding Glacial acetic acid solution in distilled water and then soaking chitosan in acetic acid solution for about 12 hrs to allow complete hydration of chitosan then volume of the chitosan solution was adjusted to approximately 80% of the weight of MCC to be taken for the experiment, which was optimized on the basis of liquid intake capacity of MCC PH 102. Finally the chitosan solution was mixed properly by stirring under the mechanical stirrer for about 30 min. at 500 RPM.

FDG were prepared by granulating directly the weighed quantity of MCC with the complete quantity of chitosan solution and sufficient kneading to get dense wet mass which was partially dried in tray dryer at about 50 °C and passed through #18mesh sieve (1000 µ) and allowed to completely dry at 60°C (till the moisture level reaches below 5% w/w) in tray dryer. The dried granules then passed through #40 mesh sieve (425 µ) completely, collected and labelled.

2.2 Blending:

Required quantities of extra granular excipients i.e. Chitosan, Aspartame, Citric acid, Menthol and the drug Cinnarizine were first sifted through # 40 mesh sieve (250µ) and mixed with the accurate amount of FDG by hand blending in a polyethene bag for 10 min. then separately the weighed and sifted (through #60 mesh) Colloidal silicon dioxide and Magnesium stearate were added and mixed in the same way for 2 min each to get the final granules to be compressed to an ODT containing around 8.33% w/w of Cinnarizine.

2.3 Powder Characteristics:[14,15]

Angle of repose was determined by conventional funnel method. The blend was poured through a funnel fitted at appropriate distance from the base, till the blend achieves maximum cone height (h in cm) was obtained. Radius of the cone (r in cm) was measured, which is the average of 3 different radius of the heap circle and the angle of repose (q) was calculated using the formula:

$q\ (°) = \mathrm{Tan}^{-1}\ (h/r)$ . . . .(1)

Angle of repose below 25° states a good flow property are always desired.

Apparent bulk density (BD) was determined by pouring the weighed (W in g) amount of the blend into a graduated cylinder. The bulk volume (V in ml) of the blend was determined. The bulk density was calculated using the formula:

$BD\ (gm/ml) = W/V$ . . . . . (2)

The tapped density (BD) was determined by pouring the weighed (W in g) amount of the blend into a graduated cylinder and the blend was tapped for a fixed time with uniform force. The final volume (Vf in ml) occupied in the cylinder was determined measured and The tapped density was calculated using the following formula:

$TD\ (gm/ml) = W/\ Vf$ . . . . . (3)

The simplest way for measurement of free flow of powder is compressibility index, an indication of the ease with which a material can be induced to flow is given by compressibility index (CI) which is calculated as follows:

$CI\ (\%) = 100 * (V\text{-}Vf/V)$. . . . . (4)

Where, V (in ml) is the bulk volume and Vf (in ml) is tapped volume of the blend. The value below 15% indicates a powder with good flow characteristics.

Hausner's ratio (HR) is an indirect index of ease of powder flow, can be calculated by the following formula:

$HR = TD/BD$. . . . . (5)

Where TD (in g/ml) is tapped density and BD (g/ml) is bulk density, lower Hausner's ratio below 1.2 indicates better flow properties of the blend.

2.4 Compression of tablets and evaluation: [16,17]

Around 100 Tablets per batch were compressed from the uniformly mixed blend using single station tablet press using round flat faced punches of 9 mm diameter with an average weight of 300 mg.

Weight Variation

Twenty tablets were selected at a random and average weight (weighed using AND analytical balance) was determined. Then individual tablets were weighed and compared with average weight.

Friability

Friability of 10 tablets was determined using friability test apparatus (Electrolab, Mumbai). This apparatus tests

the tablets for the combined effect of abrasion and shock in a transparent chamber revolving at 25 rpm by dropping the tablets at a height of 6 inches in each revolution to be run for at least 100 revolutions so as to mimic the possible handling and transportation effects that can happen during the shelf life of the tablets. For testing the tablets preweighed (W1 in g) sample of tablets was placed in the friabilator and were subjected to revolutions. Tablets were dedusted using a soft muslin cloth and reweighed (W2 in g). The % friability (F) can be given by the formula:

$$F (\%) = (1- W1 / W2) \times 100. \quad (6)$$

Crushing strength

Hardness or tablet crushing strength (CS) is the force (required to break a tablet in a diametric compression) was measured using Monsanto hardness tester. The crushing strengths of six tablets per batch at each compression force i.e. 0.5 Ton, 1.0 Ton and 1.5 Ton levels were determined in Kg/cm^2.

Disintegration time[18]

The disintegration time of the water dispersible tablets was determined in accordance with the IP monograph of Dispersible tablets, stating a maximum disintegration time of 3 min for dispersible tablets. The disintegration apparatus (Electrolab DTA, India) was used. The medium consisted of water at a temperature between 25 ± 1 °C. Only one tablet at a time was tested and considered disintegrated when completely dispersed fragments were obtained, total 6 units were tested for each trial batch and mean disintegration time was calculated.

Wetting time

A conventional method was used to measure wetting time and capillarity of the ODTs. The tablet was placed in a Petri dish of 5.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out in triplicate and the mean value was calculated.

Uniformity of Dispersion test

This test was carried out according to IP 1996, applicable only to Dispersible Tablets in which 2 tablets together are to be placed in 100 ml of water and to be stirred gently until completely dispersed. A smooth dispersion is to be obtained which should pass through a sieve screen with a nominal mesh aperture of 710 µm (ASTM #25).

Percent Porosity

The percent porosity of the tablets was calculated as follows:

$$\% P = 100 * \{1 – (LV - CV /LV)\}. \quad (7)$$

Where P is the porosity of the tablet, LV is the loose volume (in mm^3) of the blend obtained by measuring the volume of preweighed blend using a measuring cylinder and calculated for 300 mg blend weight, CV is the volume (in mm^3) of compressed tablet of weight 300 mg the dimensions of tablets were measured using a Vernier calliper (0.01-mm precision, Mitutoyo, Japan) and the volume of the tablet was determined by using the formula as follows:

$$V = \frac{\pi * H * D^2}{4000} \quad (8)$$

Where V is the Volume of tablet, H (in mm) is the thickness of tablet and D (in mm) is the diameter of the tablet.

Drug Content

Ten tablets were powdered and the blend equivalent to 25 mg of Cinnarizine was weighed and dissolved in suitable quantity of methanol. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically (UV-1700, Shimadzu, Japan) at 253 nm against the standard solution of known concentration. Samples were analyzed in triplicate.

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a 10 ml beaker containing 6ml of buffer solution simulating saliva fluid (pH 6.8) and time required to disperse the tablet completely was noted.

Invitro dissolution studies

In vitro dissolution studies for all the formulated tablets was carried out using paddle method at 75 rpm in 900 mL of 0.1 N HCl and pH 4.6 Acetate Buffer IP separately as dissolution media, maintained at 37° ± 0.5°C and 5 mL aliquot was withdrawn at the specified time intervals (5, 10, 15 and 30 minutes), filtered through whatman filter paper and after suitable dilutions analysed spectrophotometrically (UV-1700, Shimadzu, Japan) for drug content at 253 nm. An equal volume of pre-warmed (37°C) fresh medium was replaced into the dissolution medium after each sampling, to maintain the constant volume throughout the test. Dissolution studies were performed on 6 units for all the batches.

In vivo Disintegrating Time[19]

For determination of the in vivo disintegration time, six healthy human male volunteers, from whom informed consent was first obtained, randomly took one CODT without drinking water and the time required for complete disintegration of the tablet in the mouth without biting was measured. Immediately after the in vivo disintegration test, volunteers rinsed their mouth without ingesting the disintegrated particles.

2.5 Experimental design

The composition of the CODT was first conceptualized on trial and error basis doing prior feasibility experiments considering dispersion in water, crushing strength (CS) and the wetting time (T_{wet}) as critical parameters to be observed and the optimum concentration of CGL and CXG was determined for the good behaving tablet composition i.e. with optimum % porosity, good CS and minimum T_{wet} for further experimentation. Details of initial batches taken are given in Table I.

2.6 Design matrix evaluation for Response Surface quadratic model

A 3 way full factorial randomized design was implemented for the optimization of the CODT. Dependent response factor variables measured were wetting time (T_{wet}), disintegration time (DT), Time to

achieve 90% dissolution ($T_{90\%}$), percent porosity (P) and crushing strength (CS). Three independent factors, the concentration of chitosan in granulating liquid (CGL) and the concentration of chitosan in extra-granular excipients (CXG) and the compression force (CF), were set at three different levels. High and low levels of each factor were coded as 1 and −1, respectively, and the mean value as zero. The range of a factor must be chosen in order to adequately measure its effects on the response variables. As per the data obtained from trial batches (Table I), duplicated formulations C8 and C9 were selected for the 3 level full factorial randomized design, in this design 3 factors were evaluated, each at 3 levels, and experimental trials were performed at all 27 possible combinations and additionally centre point combination was repeated 5 times to ensure the precision. The independent factors selected were the amount of CGL, the amount of CXG and the CF in values of (9.0 mg, 18.0 mg and 1.0 Ton respectively) on the basis of selected composition were considered as the centre point for 3 level factorial designs and the composition was optimized, details of the factor and factor levels are given in the Table II as physical units. Centre points were repeated five times to estimate the experimental error.

3. RESULTS AND DISCUSSION

Preliminary trials were taken (method as described earlier) to prove the concept of using chitosan as superdisintegrant hence the effectiveness of chitosan as a superdisintegrant was checked. Observations for initial trials as per Table III revealed that the batches without chitosan (C1) in which only MCC has been used as overall bulking material along with some of the auxiliary excipients could not even produce the complete disintegration though the flow properties of the blend was good enough due to the presence of high amount of MCC but hardness of the tablet was very less and other desirable parameters for the ODT were not acceptable. Similar observations were obtained for the further two batches with chitosan but one with chitosan used as granulating fluid (CGL) in trial (C2) and another with chitosan used as extra-granular material (CXG) in trial (C3). It was considered that the amount of chitosan to be used should be as low as possible as it has to be tested for the superdisintegrant properties so minimum quantities of chitosan were taken for the preliminary batches i.e. only 2% and 3% of the tablet weight for (C2) and (C3) respectively. The only difference observed was the hardness was improved for the trial (C2) whereas the flow property of the trial (C3) was drastically altered which revealed that the amount of CGL is necessary for the good mechanical strength of the tablets but if the amount is completely provided as CXG it could impair the flow property of the blend. Compression Force (CF) for the preliminary trial batches (C1 to C9) was kept constant at 1000 psig (1 Ton) so as to nullify the effect of CF on the ODT parameters. For the further batches (C4), (C5) and (C6) both the types of chitosan were added to the formulations starting with the minimum amount which revealed that the presence of both the forms of chitosan i.e. in granulating liquid and as extra-granular material is must for imparting the disintegration property to the tablets. Also it was observed that despite the increase in the quantity of the chitosan in both the forms the dispersion and wetting properties of the tablets are improving and at the same time the hardness of the tablet has been found improving as the CGL quantity has been increased but at the same time it has been found that the increased amount of CXG is responsible for the more improvement of dispersion and wetting properties of the tablet are highly desirable for the ODTs. Trial (C7) was taken to minimize the quantity of glidant (Colloidal Silicon dioxide) and lubricant (Mg. Stearate) in the tablet without disturbing the ODT properties and it was found considerably working with the reduced amount of glidant and lubricant. Trials (C8) and (C9) were taken with the increased quantities of CGL and CXG in duplication to access the reproducibility of the formulation and found that the further improvement in ODT properties and increased mechanical strength of the tablets. Chitosan based CODT were prepared and optimized on the basis of response surface methodology and were evaluated for the various desirable ODT parameters. The various in vitro tests and in vivo disintegration test in healthy human volunteers represented the ideal ODT formulation in all respects including the role of Cinnarizine as a model drug candidate too was justified.

Experimental trials were performed for all 27 possible combinations as per the factorial design described in Table II and additionally centre point combination was repeated 5 times, the various ODT parameters in form of the dependent variables were evaluated and tabulated in Table IV. All the batches were prepared according to the desired independent parameters and evaluated for the different dependent parameters desired for ODT to get the response as per the factorial design and to obtain the optimized formulation which can further be evaluated completely for the various tablet characteristics. A quadratic 3 level factorial design response surface methodology was performed to evaluate the observations. A three level experimental design provides sufficient data to fit a second-degree polynomial analysis for various dependent factors like T_{wet}, DT, $T_{90\%}$, CS and %P. Degrees of Freedom (DF) for Evaluation observed was 17 for Lack of Fit (LOF), where minimum 3 DF was desired which ensures a valid lack of fit test. A DF of 5 for Pure Error was obtained, where a minimum of 4 DF was desired hence the design was found to be acceptable. All tests were performed at a 95% level of significance (α=0.05) for which Power should be approximately 80% for the effect to be detected. The adequacy of the final quadratic models was examined by Fit summary, analysis of variance (ANOVA), and response Graphs. All the statistical analyses and optimization for the best composition were performed using Stat Ease Design Expert® (Version 7.1.1) software. On the basis of the results obtained from the Factorial design trials and the various assumptions put in the form of constraints for the

optimization solution exercise, the Constraints are discussed in Table V. Solutions with their desirability were obtained from the Design Expert software, out of around 21 possible solutions the one best desired solution is given in Table VI which was formulated and used for further characterization as given in Table VII. As the tablets were prepared using wet granulation technique, the powder material was free flowing with good compressibility, tablets were obtained of uniform weight and variations within Pharmacopoeial specifications. The drug content was found in the acceptable range. The hardness of the tablets between 3.3 - 4.2 kg/cm^2. Friability of the tablets were found below 1% indicating a good mechanical resistance of tablets and all the parameters were found well within the specified limit for uncoated dispersible tablets. In vivo dispersion test was also performed in 6 healthy male volunteers and observed that all the volunteers found the formulation well disintegrating and providing good mouth feel and dispersion time noted for individual volunteers were very close to each other giving very less standard deviation, mean value given in Table VII.

Dissolution profiles for the optimized formulation in two different media are presented here, depending on the solubility of the drug the dissolution media were selected as the drug is practically insoluble in higher pH above 5, it has been tested for dissolution profile in acidic medias like 0.1 N HCl and 4.6 pH acetate buffer IP as in Fig. 1. In vitro disintegration in Fig. 2 show that the optimized formulation disintegrates in about 50 sec. preferred for an ODT.

Responses for the dependent variables

The statistical analysis of the factorial design batches was performed by quadratic modelling using Design Expert. The Twet, DT, T90, CS and %P for 27 + 5 batches (Trials 1 to 32) showed a wide variation for which the results are shown in Table IV. The data clearly indicate that the values of dependent variables are strongly dependent on the independent variables. The mathematical relationship constructed for the studied response variables are expressed as Eqns. 2, 3 and 4. All the polynomial equations were found to be statistically significant ($P < 0.05$) as determined by ANOVA. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient with positive or negative signs.

$$T_{wet} = 29.82 - 4.72 * A - 4.94 * B + 6.67 * C + 1.00 * A * B + 2.08 * A * C - 1.17 * B * C - 0.71 * A^2 - 3.04 * B^2 + 1.12 * C^2 \quad (9)$$

$$DT = 14.65 + 5.33 * A - 2.06 * B + 7.06 * C + 0.083 * A * B + 2.42 * A * C - 0.92 * B * C + 7.25 * A^2 - 1.25 * B^2 + 2.41 * C^2 \quad (10)$$

$$T_{90\%} = 6.45 + 1.67 * A - 1.39 * B + 1.67 * C + 0.000 * A * B - 0.42 * A * C - 0.42 * B * C + 2.47 * A^2 - 0.027 * B^2 + 0.81 * C^2 \quad (11)$$

$$CS = 2.83 + 0.33 * A + 0.39 * B + 0.86 * C \quad (12)$$

$$\%P = 29.69 + 1.44 * A - 3.61 * B - 7.72 * C \quad (13)$$

Where A stands CGL in mg, B stands for CXG in mg and C stands for CF in Kg/cm^2. All the equations are found to be significant as per the desired F-values, P value <0.0001 and found suitable to be implemented as the Pred R-Squared is in reasonable agreement with the Adj R-Squared and adequate Precision which measures the signal to noise ratio is well above 4 for all the equations hence all the models found to be suitable to navigate the design space. The response graphs in Fig. 3 shwo the effect of various independent variables, on seperately all the dependent variables whcih accordingly interpreted.

Wetting time (T_{wet}): This test mimics the action of saliva in contact with the tablet. The response analysis describes the relationship between the wetting time and the independent variables by the following response graph (Fig. 3). Wetting time showed the direct correlation with the hardness (CS) of the tablet i.e. wetting time also increases with the increase in hardness of the tablet that is why the response graph seems to be flat as the CF has been taken as fixed 1.0 Kg/cm^2, also wetting time found to be decreased (which is desirable) with the increase in the content of CGL hence it can be predicted that the CGL increases the hydrophilicity of the tablet and increases the capillary action. Although amount of CXG did not impart much influence on the wetting time directly but as it reduces the hardness of the tablet may indirectly reduce the wetting time of the tablet hence an increased amount of both the forms of chitosan (CGL and CXG) are desirable to reduce the wetting time of the tablet which leads to the fast disintegration of the tablet in oral cavity. Also as per the response graph it is clear that too high concentration of CGL and CXG are not desirable hence optimum concentrations of both the independent factors are desired for good ODT properties.

Disintegration time (DT): This parameter gives the virtual idea of how fast the disintegration of an ODT will occur in oral cavity hence the DT should be as low as possible and the ideal DT should be less than 10 seconds for ODT (Fig. 3). Although a significant impact of all the independent factors viz. CGL, GXG and CF can be visualized by the response graph but the effect of CXG on DT is quite less at the same time there is influencing effect of CGL can be observed on DT as the DT is proportionately increasing upon increase in CGL. Also it has been noted that the too high a quantity of CGL can further retard the DT of tablet which can be justified with the fact that the CGL is responsible for the good Crushing strength hence if CS is too high means the maximum mechanical strength of the tablet leads to the increased DT which is not desired for an ideal ODT. Although wicking action of CXG can counter the effect of CF as it is clear from the response graph that the increase in CF did not increase DT by a proportional rate. As the DT is the typical requirement of an ODT the quantity of the independent factors hence need to be put in optimum range.

Time require for 90% drug release ($T_{90\%}$): It is assumed that if 90% of the drug is released in the dissolution media, it will exert its full effect in-vivo hence in case of ODTs it is desirable to get the maximum amount of drug dissolved in minimum time possible so the dissolution test was performed as per described in earlier section and the time to reach the drug release to 90% was determined to optimize the formulation as per response in Fig. 3. Dissolution test is not the basic parameter for and ODT to optimize as the dissolution of a conventional non disintegrating tablet could be achieved within 5 minutes of the dissolution test hence it is always desirable to get the minimum $T_{90\%}$ of an ODT for the purpose of fast symptomatic relief for which an ODT has been formulated. Though the desired $T_{90\%}$ for the proposed ODT is less than 5 min. the dissolution test has been performed for a time up to 15 min. and 5, 10 and 15 min. were taken as the dissolution time points. Only those combinations which are having a very high CF or those which contain a very less concentration of CGL and CXG were found to have a higher i.e. 15 min as $T_{90\%}$ from which it is clear that the $T_{90\%}$ is inversely proportional to the CF and an optimum amount of CGL and CXG are desired for minimum $T_{90\%}$.

Crushing strength (CS): The crushing strength of the tablets varies within a wide range of 1.5 to 4.5 Kg/cm^2 therefore, several formulations are not acceptable for their mechanical strength in Fig. 3. CS is the basic parameter required for and ODT as generally observed CS is being compromized for the formulation of an ODT with faster dispersion and disintegration as the low CS produce high porosity in the tablet and hence very less DT and fast disintegration in oral cavity too. From the response graph it is evedant that the CS is directly proportional to the all of the independent variables as the model equation is also linear in nature leading to the higher CS for higher amount CGL and CXG will be observed and also it is very obvious that higher the CF higher will be the CS of an ODT. But at the same time higher values of all the independent parameters can not be put for an optimized formulation as the same can hamper the other desirable properties of and ODT like DT and T_{wet}. In contrast to other depended factors, higher value of CS (i.e. maximum CS) is desired compared to the lower values requied for other dependent variables.

Percent Porosity (%P): Influence of porosity on disintegration time is inversely proportional, DT decreases as the porosity increases but at the same time mechanical strength of the tablet is also decreases with the increase in porosity hence an optimum porosity is required which allows a fast DT with a good mechanical strength too as per Fig. 3. % P is the parameter which does not produce the major impact on the various desirable properties of ODT except the wetting time and at the same time is very slightly but linearly dependent on the various independent factors which can be seen from the response graph. Also it is observed that the %P is directly proportional to the CGX as CGX provide the more porous tablets as compared the CGL since it gives more dense granules to give more compact tablets hence less porosity. Ideally a highly porous tablet is desired for getting a good behaving ODT but for this factorial design we intended to keep the lowest possible %P as the dependent factor since we wanted not to compromise with the CS of the tablet as a high %P will give the less CS tablets.

CONCLUSION

From the investigation, it can be demonstrate that it is possible to develop CODT by a simple wet granulation process with chitosan as superdisintegrant utilizing a 3 level full factorial design, with acceptable parameters required for ODTs, in order to improve disintegration and dissolution of the drug in oral cavity and hence better patient compliance and effective therapy. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption of Cinnarizine leading to its increased bioavailability. Chitosan based ODT technique would be an effective alternative approach to the use of more expensive superdisintegrant adjuvants in the formulation of mouth dissolving tablets. Moreover the results suggest that development of mouth-dissolving tablets of Cinnarizine without any common superdisintegrants can be achieved using chitosan based technology. Similar to the other superdisintegrants, chitosan too generously engulf water when in contact with aqueous media and burst due to the pressure exerted by their capillary action thereby impart instantaneous disintegration of the dosage form and resulting in formation of a uniform dispersion in the surrounding media which behave like a true suspension formed inside the body leading to rapid and complete absorption of drug. chitosan based CODT exhibited good in vitro dispersion and wetting properties without compromising the mechanical strength of the tablets, thus the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance specially in case of children and elderly patients in the form of CODT. In conclusion, we succeeded in confirming that the preparation method designed in this research is scalable, industrially applicable and useful for the preparation of ODTs containing drugs with poor solubility and poor bioavailability.

Table I: Details of preliminary trials for proof of concept studies.

Sr. No.	INGREDIENTS	C1 (mg)	C2 (mg)	C3 (mg)	C4 (mg)	C5 (mg)	C6 (mg)	C7 (mg)	C8 (mg)	C9 (mg)
1	MCC PH 102	251	241	242	232	227	221	224	221	212
2	Chitosan	0	6	0	6	9	9	9	9	9
3	Acetic Acid Glacial	0	4	0	4	6	6	6	6	6
4	Chitosan	0	0	9	9	9	15	15	18	18
5	Aspartame	6	6	6	6	6	6	6	6	6
6	Citric acid	6	6	6	6	6	6	6	6	12
7	Menthol	6	6	6	6	6	6	6	6	9
8	Cinnarizine	25	25	25	25	25	25	25	25	25
9	Colloidal Silicon dioxide	3	3	3	3	3	3	1.5	1.5	1.5
10	Mg. Stearate	3	3	3	3	3	3	1.5	1.5	1.5
	Tablet Wt. (mg)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Table II: Selected factor levels for the experimental design for optimization of CODT

Factor Details			Factor Level		
Code	**Actual**	**Unit**	**-1**	**0**	**+1**
A (CGL)	Chitosan in Granulation liquid	mg	6	9	12
B (CXG)	Chitosan extra granular	mg	15	18	21
C (CF)	Compression Force	Kg/cm^2	0.5	1.0	1.5

Table III: Observations of blend and tablet evaluation for preliminary feasibility trials.

PARAMETERS	C1	C2	C3	C4	C5	C6	C7	C8	C9
Powder Characteristics									
Angle of Repose (°) #	28.54 ±0.68	26.36 ±0.22	25.29 ±0.25	32.48 ±0.29	29.89 ±0.18	27.33 ±0.96	28.67 ±0.53	24.08 ±0.26	24.22 ±0.38
Bulk Density (g/cm^3) #	0.434 ±0.47	0.452 ±0.38	0.386 ±0.94	0.463 ±0.37	0.452 ±0.85	0.461 ±0.22	0.472 ±0.47	0.478 ±0.23	0.481 ±0.84
Tapped Density (g/cm^3) #	0.525 ±1.08	0.602 ±0.96	0.571 ±0.96	0.589 ±0.67	0.581 ±0.83	0.588 ±0.38	0.572 ±0.95	0.567 ±0.74	0.569 ±0.63
Compressibility Index (%)	17.33	24.92	32.40	21.39	22.20	21.60	17.48	15.70	15.47
Hausner's ratio	1.21	1.33	1.48	1.27	1.29	1.28	1.21	1.19	1.18
Tablet Evaluation									
Dispersion time (sec.) #	IC	IC	IC	130 ±0.44	110 ±0.54	90 ±0.27	88 ±0.68	75 ±0.99	60 ±0.65
Wetting time (sec.) #	70 ±0.35	60 ±0.28	55 ±0.69	50 ±0.16	46 ±0.84	41 ±0.30	40 ±0.46	30 ±0.47	32 ±0.68
Crushing Strength (Kg/cm^2) *	1 ±0.29	2 ±0.50	1 ±0.29	1.5 ±0.29	2 ±0.50	2 ±0.29	2 ±0.27	2.5 ±0.17	2.5 ±0.18
% Porosity (w.r.t. Powder)	47	38	45	35	32	32	30	29	30
Remarks (Acceptability)	No	No	No	No	No	No	No	Yes	Yes

is the mean of 3 values ± SD
* is the mean of 6 values ± SD
IC: In Complete dispersion (i.e. dispersion time more than 3 min.)

Table IV: Observations of ODT parameter evaluation for factorial design trials.

Std.	Run	Independent Variables			Dependent Variables				
		CGL (mg)	CXG (mg)	CF (Ton)	T_{wet} (Sec)	DT (Sec)	$T_{90\%}$ (Min)	CS (Sec)	Porosity (%)
1	20	6	15	0.5	30	14	5	1.5	42
2	24	9	15	0.5	27	11	10	1.5	40
3	26	12	15	0.5	17	20	10	2	40
4	8	6	18	0.5	28	12	5	1.5	38
5	1	9	18	0.5	27	12	5	2	36
6	23	12	18	0.5	15	19	10	2	35
7	18	6	21	0.5	24	10	5	1.5	37
8	15	9	21	0.5	16	10	5	2.5	34
9	31	12	21	0.5	12	18	10	2.5	32
10	6	6	15	1	36	18	10	2	30
11	10	9	15	1	34	16	10	2.5	36
12	12	12	15	1	22	25	10	2.5	33
13	21	6	18	1	33	16	10	3	25
14	22	9	18	1	31	13	5	3.5	29
15	9	12	18	1	20	24	10	3.5	35
16	14	6	21	1	25	13	5	2.5	31
17	16	9	21	1	18	11	5	4	17
18	25	12	21	1	18	23	10	4	45
19	29	6	15	1.5	45	27	10	3	31
20	7	9	15	1.5	38	21	10	3.5	18
21	27	12	15	1.5	39	45	15	3.5	36
22	28	6	18	1.5	41	24	10	3.5	18
23	13	9	18	1.5	31	19	10	3.5	15
24	4	12	18	1.5	36	42	15	3.5	32
25	3	6	21	1.5	31	22	10	3.5	21
26	30	9	21	1.5	26	17	5	4	13
27	32	12	21	1.5	29	36	10	4.5	11
28	19	9	18	1	31	18	5	2.5	30
29	2	9	18	1	30	16	5	2.5	32
30	17	9	18	1	30	17	5	2.5	29
31	5	9	18	1	33	15	10	3	23
32	11	9	18	1	34	16	5	3	26

Table V: Constraints set for Response Surface Methodology optimization solution.

Factor	Factor type	Goal	Lower Limit	Upper Limit	Importance
CGL	Independent	Should be in range	6	12	5
CXG	Independent	Should be in range	15	21	5
CF	Independent	Should be in range	0.5	1.5	3
T_{wet}	Dependent	Minimum possible	12	45	5
DT	Dependent	Minimum possible	10	45	5
$T_{90\%}$	Dependent	Minimum possible	5	15	3
CS	Dependent	Maximum possible	1.5	4.5	5
% Porosity	Dependent	Minimum possible	11	45	2

Table VI: Showing details of the optimized formulation as per response methodology.

Factors	CGL	CXG	CF	T_{wet}	DT	$T_{90\%}$	CS	% Porosity	Desirability
Values	9.05	21	1.11	23.05	12.90	5.38	3.41	24.40	0.747

Table VII: Evaluation of Optimized formulation and their results.

Evaluation of Optimized Formulation for Physical and Chemical Parameters (Result are mean values ± SD)				
Average Wt. (mg) n = 10	**% Wt. Variation n= 10**	**Thickness (mm) n = 10**	**Friability (%) n = 10**	**% Drug content n = 3**
300.2 ± 0.42	+ 2.4 to - 3.6	4.62 ± 0.07	0.68 ± 0.24	99.8 ± 0.19
Evaluation of the Optimized Formulation for ODT Parameters (Result are mean values ± SD)				
Crushing Strength (kg/cm^2) n = 6	**Wetting time (s) n = 3**	**Disintegration time (s) n = 3**	**Time for 90% drug release (min.) n = 6**	**In vivo dispersion time (s) n = 6**
3.5 ± 0.29	19 ± 0.58	11 ± 0.62	5.0 ± 0	46 ± 0.38

Fig 1: Dissolution profile of CODT (optimized formulation) in two different media.

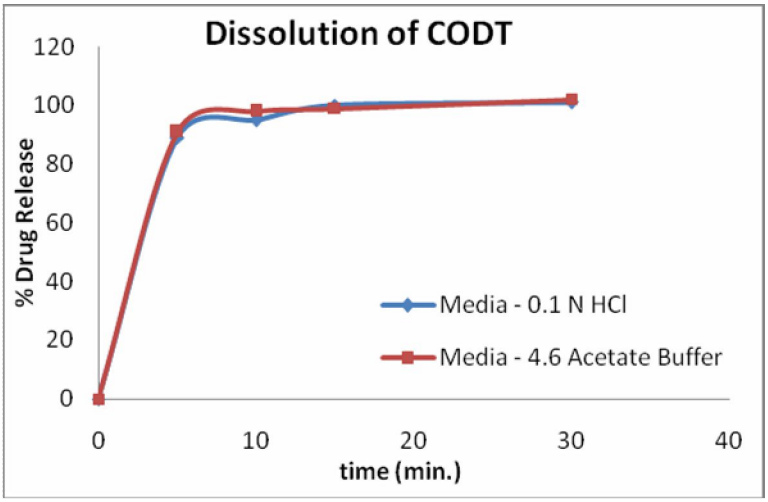


Fig 2: Photographs of various stages of disintegration of a CODT in water. The chronological sequence is presented along with the disintegration time in seconds.

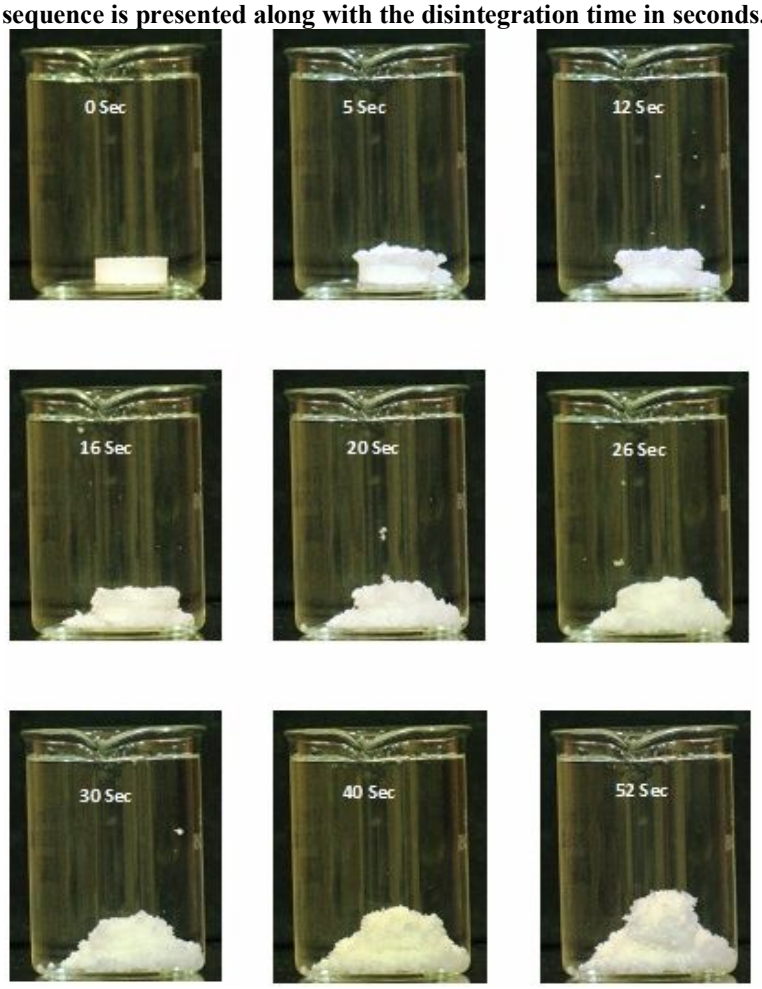
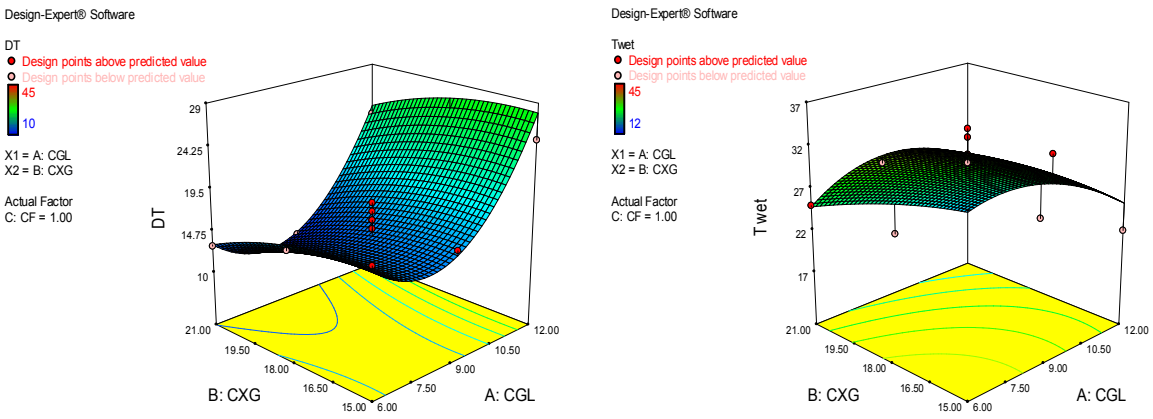
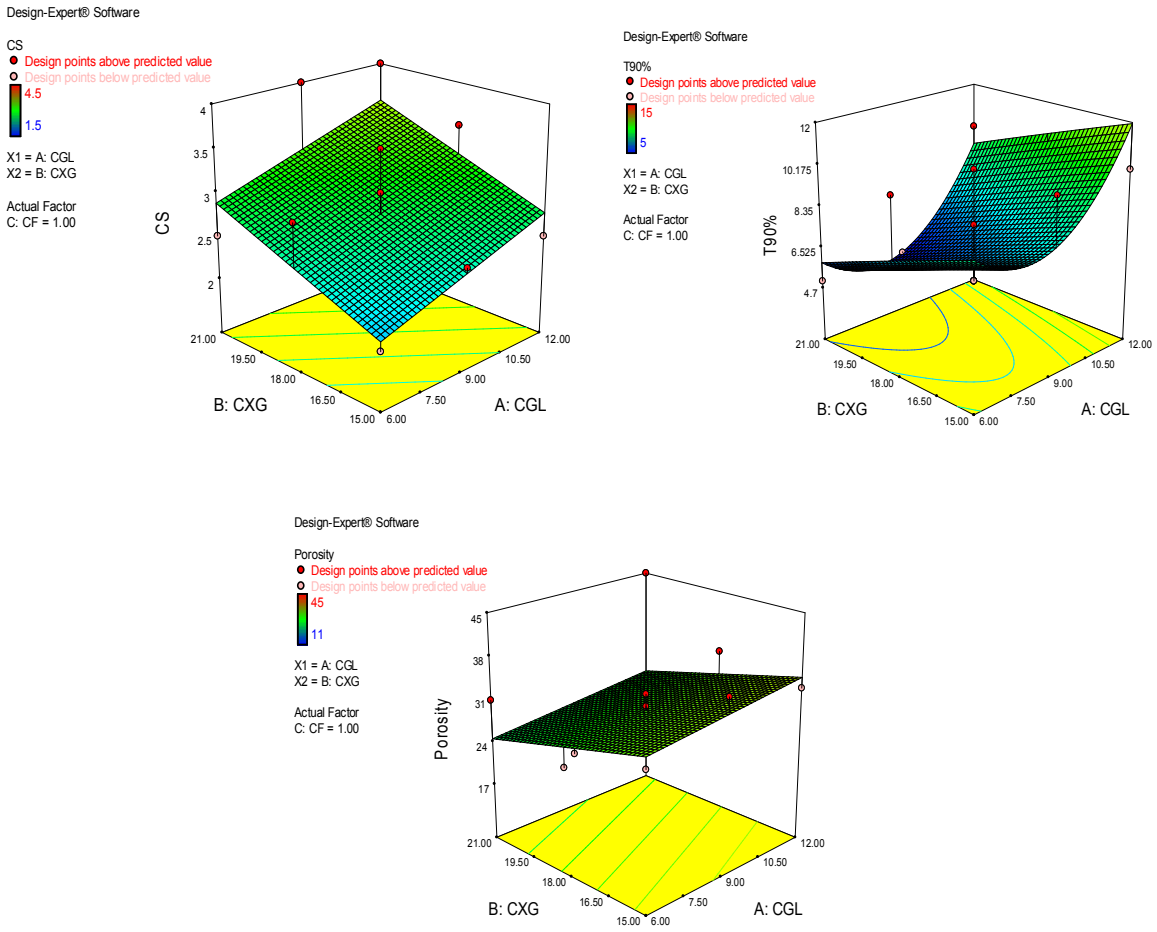


Fig 3: Response Graphs of optimized formulation for T_{wet}, DT, $T_{90\%}$, CS and %P.





REFERENCES

1. Tapash K. Ghosh and William R. Pfister Edited, Drug Delivery to the Oral Cavity: Molecules to Market, Taylor & Francis Group, FL, USA, 2005, 261-290.
2. Biradar S. S., Bhagavati S. T., Kuppasad I. J., Fast Dissolving Drug Delivery Systems, A Brief Overview, Int. J. of Pharm., 2006, 4, 2.
3. Mizumoto T, Masuda Y, Fukui M, Intrabuccally dissolving compressed molding and production process thereof, U.S. Patent 5,576,014.
4. Virley P, Yarwood RJ. Zydis, A novel fast dissolving dosage form, Chemist 1990, 61 (2) 36−37.
5. Wehling F, Schuehle S, Madamala N. Effervescent dosage forms with microparticles, U.S. Patent 5,178,878.
6. Wehling F, Schuehle S., Base coated acid particles and effervescent formulations incorporating same, U.S. Patent 5,503,846.
7. Myers GL, Battist GE, Fuisz RC., Delivery of controlled release systems, U.S. Patent 5,567,439.
8. Cherukuri SR, Myers GL, Battist GE, Fuisz RC, Process for forming quickly dispersing comestible unit and production therefrom, U.S. Patent 5,587,172.
9. Habib W., Khankari R. and Hontz J., Fast-dissolve drug delivery systems. Crit. Rev. Ther. Drug Carrier Syst., 2000, 17, 61–72.
10. Vishnu Patel, Madhabhai Patel, Rakesh Patel, Chitosan: A Unique Pharmaceutical Excipient, Drug Delivery Technology, June 2005, 5, 6.
11. Mia Sakkinen, Biopharmaceutical evaluation of Microcrystalline cellulose as release rate controlling hydrophilic polymer in granules for gastro retentive drug delivery, Heilsinki Thesis, 2003, 1-9.
12. Sweetman S. Edited, Cinnarizine, Martindale: The Complete Drug Reference, 34th Edition, Phamracy Press, London, 428.
13. CIMS 102 India, July – Oct 2008, Update 3, 180.
14. Marshall K., In, Lachman L., Liberman H.A., Kanig J.L. E, Eds., The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese publishing house, India, 1987, 66-99
15. Lindberg N., Palsson M., Pihl A., Freeman R., Freeman T., Zetzener H. and Enstad G., Flowability

measurements of pharmaceutical powder mixtures with poor flow using five different techniques, Drug Dev. Ind. Pharm. 2004, 30 (7), 785-791.
16. General monograph of Tablet, Indian Pharmacopoeia, 1996.
17. Banker G. S., Anderson N. R., In, Lachman L., Liberman H.A., Kanig J.L. E, Eds., The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese publishing house, Mumbai, 1987, 293-345.
18. Kimura S, Imai T, Otagiri M, Pharmaceutical evaluation of Ibuprofen syrup containing low molecular weight gelatin. J. Pharm. Sci. 1992, 81: 141-144.
19. Tatsuya Ishikawa, Yoshiteru Watanabe, Naoki Utoguchi, and Mitsuo Matsumoto, Preparation and Evaluation of Tablets Rapidly Disintegrating in Saliva Containing Bitter-Taste-Masked Granules by the Compression Method, Chem. Pharm. Bull., 1999, 47(10) 1451—1454.

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