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Preparation and evaluation of orodispersible tablet of Aripiperazole

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Abstract: Aripiprazole is a bitter drug, freely soluble in organic solvents but it is practically insoluble in water & its solubility is pH dependent. Therefore, In order to ensure adequate bioavailability, aripiprazole and betacyclodextrine are subjected to three different weight ratios (B5 1:1, 1:1.5, and 1:2).ARP-BCD complexes, are prepared by solid dispersion technique to improve dissolution & bioavailability of this poorly water soluble drug. Batch B5 (ii), in which the drug was complexed with β-Cyclodextrin in the ratio (1:1.5) shows 100% drug release within 60 minutes & it releases above 90% drug within 10 minutes .Wet granulation technique was implemented to compressed tablets of best resulted ARP-BCD complex B5 1:1.5(B6), Finally the compressed tablets were evaluated for their different parameter, like, crushing strength, friability, disintegration time, and dissolution, **In vivo disintegration time, Bitterness Index**, resulted a successful formulation. .Batch B6 (iv) the combination of MCC (ceolus KG 802) & xylitol as a filler shows best disintegration characteristics, acceptable friability, good mouth feel, sufficient hardness and 100% dissolution profile. To the optimized batch of B6 (iv) Acesulfame potassium ,and other sweetners and flavours were added. The intensity of the bitterness was found out by comparing the bitter index level of prepared 3 batches i.e. X1, X2, and X3. .Batch X3 with 2% sweetening & flavouring agent produces tasteless tablets with good & pleasant mouthfeel.So it was concluded that by means of addition of 2% of sweetening & flavouring agent the bitter taste masking was achieved upto the required level.

Keywords:, **Aripiperazole disperszxible unit,, Taste masking of ARP, Antipsychotic drug formulation with superdisintegrants, solubil;ity enhancement of aripiperazole,, solubility enhacement, of poorly water soluble drug.**

INTRODUCTION:

DRUG INFORMATION [6,7,8,9]

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It is chemically *7-[4-[4-(2, 3-dichlorophenyl) piperazin-1-yl]butoxy]-3, 4-dihydro-1H-quinolin-2-on or* 7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl] butoxy]-3, 4-dihydrocarbostyril**ProprietaryName**-Abilify]**[Molecular formula** $C_{23}H_{27}Cl_2N_3O_2$ **][Molecular Weight :**448.385.] **Aripiperazole having** indication for the treatment of schizophrenia **.**is a white crystalline powder and is practically insoluble in water and its Solubility is pH dependent. Aripiprazole can exist in several crystalline forms, Form I was chosen for the development and commercialization. The active substance does not contain any chiral centers and does not exhibit any optical isomerism.Mechanism of action of aripiprazole is novel as it involves a combination

of partial agonist action (agonist/antagonism) at dopamine D2and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors. It is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%., can be administered with or without food. The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extra vascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99%bound to serum proteins, primarily to albumin. The drug is metabolized primarily by three biotransformation pathways. Dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. It is the predominant drug moiety in the systemic circulation. At steady state, dehydroaripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma. Approximately 25 % of aripiprazole eliminated through urine & 55% eliminated through feces.. Less than 1% of unchanged ARP was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces. Its **half–life** is75 hours for extensive metabolizer , 146 hours for poor metabolizer.

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The ideal characteristic for a drug to formulate it into an ODT dosage form is that it must possess highly soluble characteristics in water & in saliva & also it has the ability to permeate the mucosal tissue. But aripiprazole is a BCS class-II drug i.e having poor solubility & high permeability. The objective of present study is to enhace its solubility with optimum dissolution and bioavailability.

Solid dispersion technique is a commonly used technique that has been used to improve dissolution & bioavailability of poorly water soluble drugs by means of following ways

- Drug – carrier interaction
- Amorphous precipitation
- Compound or complex formation
- Wet ability enhanceation
- Reduction of aggregation & agglomeration & Solubilization of the drug by the carrier at the diffusion layer.

MATERIAL AND METHODS:

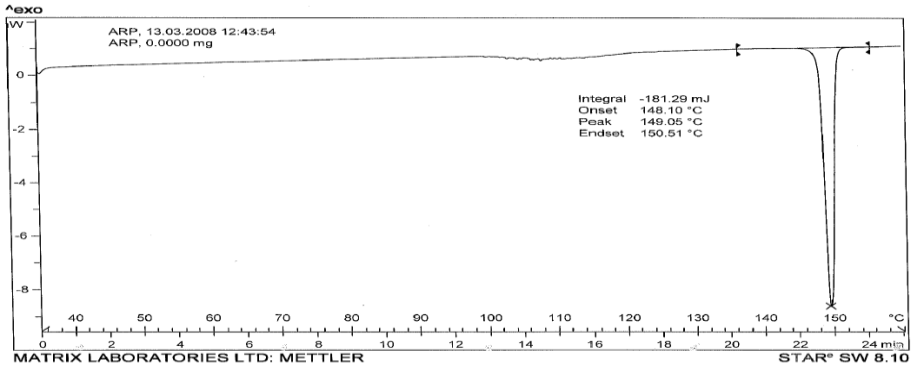
a. Material

Aripiperazole I.P, Acesulfame Potassium ,cross caramellose sodium, cross povidone, sodium starch glycolate, magnesium stearate,a erosol, xylitol, mannitol, ferric oxide red, aerosol, citric acid ,MCC PVP K 30 was obtained as a gift sample from Matrix Laboratories Ltd. Hyderabad. ,. All other chemicals and solvents were of analytical grade and used as received. Distilled water was prepared in laboratory using all glass distillation apparatus.

Methods:

NMR spectra, X-ray diffraction patterns & DSC thermograms are typically used to measure changes in the characteristics, analytical features of a drug molecule upon complexation as an indication that a complex has been formed. Dissolution profile for the drug, and complex of drug & BCD are often presented to demonstrate the influence of BCD on dissolution kinetics & the total amount of drug in solution. In addition, pharmacokinetic parameters resulting from dosing a physical mixture of drug & BCD or a preformed complex in comparison to drug alone are often presented to demonstrate an overall improvement in bioavailability upon dosing with BCD

Fig:1 (DSC report of aripiprazole: Drug (1:1.5) complexation)



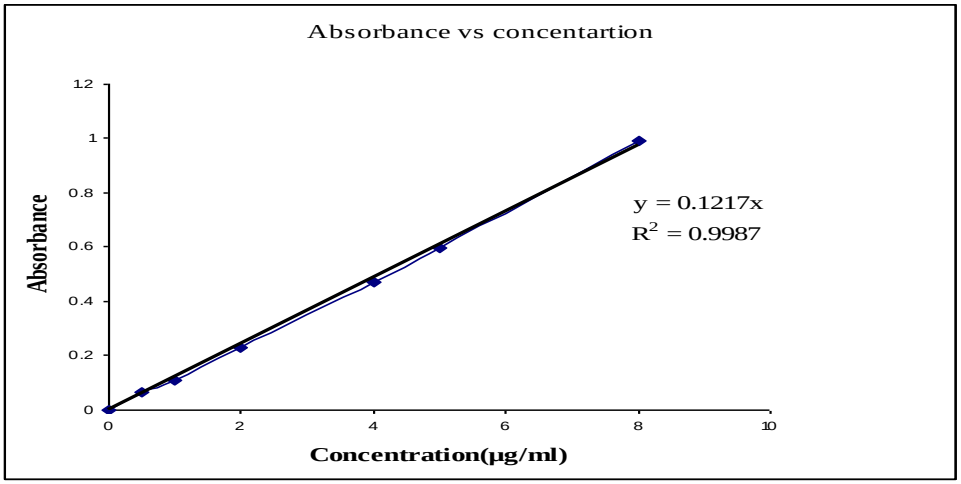
Stock solution: Aripiprazole in pH 6.8 phosphate buffer/Preparation

Accurately weighed 6.810gm of potassium dihydrogen phosphate (KH_2po4) was taken in 1lit. beaker with water content up to 500ml, to that 0.94 gm of sodium hydroxide (NaOH) pellet was added & continuously stirring by means of glass rod. Then the volume was adjusted to 1lit, & the pH was adjusted by means of sodium hydroxide.1 ml of stock solution was transferred into 1000 ml volumetric flask & the volume was made up to 1000ml with pH 6.8 phosphate buffer i.e. concentration is 10µg/ml.then the solution was further diluted to obtain 0.5,1,2,4,5,8µg/ml & their absorbance was measured UV scan was taken between the wavelengths of 200-400 nm.The spectrum is shown in figure. The absorption maxima for aripiprazole were observed at 217 nm, which was used for further studies. The concentration range & the absorbance are reported in table-1 and curve shown in graph-1

Table-1 concentration range & the absorbance Table

Concentration(µg/ml)	Absorbance
0.0	0.0
0.5	0.068
1.0	0.112
2.0	0.230
4.0	0.472
5.0	0.598
8.0	0.992

Fig-2 Standard plot of Aripiprazole in pH 6.8 phosphate buffer:



SOLUBILITY ENHANCEMENT BY COMPLEXATION WITH B-CYCLODEXTRIN BY SOLID DISPERSION METHOD AND PREPARATION OF ARIPIPERAZOLE ORAL DISPERSIBLE TABLET(ODT)

Complexation & physical mixture of ARP & BCD containing three different weight ratios (1:1, 1:1.5, and 1:2) were prepared by trituration method. Accurately weighed aripiprazole & respective weight.ratio of BCD were mixed thoroughly in a mortar, pastle by trituration continuously for 2 hrs. Then the physical mixture were passed through 40(#) & stored in desiccators for further use. Citric acid is a carrier to solid dispersion and increasing release rate.Magnesium stearate ,aerosil are libricants.PVK 130 is a binder.MCC,Cross povidone,cross caramellose sodium are intragranular proportional superdisintegrants gives better disintegrating properties compearatively. Iron oxide red is a durable inexpensive pigment.

Table-2 Formula for Preparation of Aripiprazole ODT

Ingredients	B-5(i) 1:1,	B-5(ii) 1:1.5	B-5(iii) 1:2
	Mg/tab	Mg/tab	Mg/tab
ARP-β-CD(mg)	20	25	30
Crosscarmelose sodium	14.5	14.5	14.5
Crosspvidone	7.5	7.5	7.5
MCC	95.16	90.16	85.16
PVP K30	5.25	5.25	5.25
Crosspvidone	3.0	3.0	3.0
Mg.stearate	1.5	1.5	1.5
Aerosil	0.75	0.75	0.75
Citric acid	3.0	3.0	3.0
Iron oxide red	0.015	0.015	0.015

Preparation of tablet:

B-5(ii) 1:1.5, 25 mg was compressed into tablets to Four ODT formulations **B 6 (i) B 6(ii) B 6(iii) B 6(iv)** same concentration of superdisintegrants, filler contains microcrystalline cellulose (MCC, Avicel pH 101), Xylitol, Mannitol, & a combination of MCC (Ceolous KG 802) & Xylitol respectively. Batch B6 (iv) The combination of MCC (ceolus KG 802) & xylitol as a extragranular filler shows best disintegration characteristics, Good mouth feel,Sufficient hardness, friability So the combination of MCC (Ceolus KG 802) & Xylitol based (as filler) ODT were taken for further studies. To the optimized batch of B6 (iv) Acesulfame potassium ,and other given ingredients shown in **table:** were added. The intensity of the bitterness was found out by comparing the bitter index level of the above 3 batches i.e**. X1, X2, and X3..**

From the best resulted premix **B-5(ii) 1:1.5,** 25 mg was taken & mixed with other ingredients of required amount passed through sieve (#) 40. Mixture was granulated by means of using binding solution prepared by PVPK-30 and IPA & thoroughly mixed & kneaded continuously..Then the wet mass was dried in a tray drier for 30-40 min at 40^0 C. The dried granules were passed through 30 sieves (#) & mixed thoroughly .Then the dried blend was lubricated by means of aerosol & Mg .stearate. The dried granules are continued with the Four ODT formulations **B 6 (i) B 6(ii) B 6(iii) B 6(iv) formulation process**, successively compressed into tablet by using 7.5 mm flat faced edge punch in a rotary cadmach punch machine. Finally the compressed tablets were evaluated for their different parameter. to characterise the technological properties of these different formulations ..

Tablet evaluation

Crushing strength

A Crushing strength tester (Schleuniger Hardness tester–Dr Schleuniger, Pharmatron) was used to determine the load (N) required to diametrically break the tablets into two equal halves. The crushing strength of tablets was determined after compression. Tablets with sign of lamination or capping were not used.

Determinations were made in triplicate, and the mean values are reported with 5-7kp shown in table:8

% Friability

The Crushing strength test may not be the best measure of the potential tablet behaviour during handling and packaging. The resistance to surface abrasion may be more relevant parameter in such cases. In some formulation when compressed into very hard tablets, tend to "cap" on attrition, losing their crown portions. So in that case tablet's strength can be measured by means of its friability and found in between 1%. **(table: 8)**

The percent friability of thetablets was determined using Roche friabilator operated at 25 revolutions per minute (RPM) for 4 minutes.

Twenty tablets tumbled in the friabilator after weighing them accurately. The tablets were then dedusting by soft muslin cloth and the loss in weight caused by facture or abrasion was recorded as percentage weight loss.

$$\text{Percentage Friability} = 100 \times \frac{\text{Loss in weight}}{}$$

Initial weight

Disintegration Time

The time required for disintegration of six tablets , placed in each tube of disintegration test apparatus, was measured at 37 ± 2^{o} C using 900 ml distilled water recorded as 80-100 seconds**(table:8).**

In vivo disintegration time

In measuring in vivo disintegration time, the amount of the time needed for tablet to completely disintegrate in a test subject mouth was measured. The tablet was placed on the tongue of subject and the time was recorded. The subject was instructed to gently move the tablet against the upper part of the mouth with the tongue. It is emphasized to the subject that this is a gentle motion with no biting of the tablet. Immediately after the last noticeable granule is disintegrated, the time was again recorded. Test was conducted in duplicate and average time is reported as 55-60 seconds**.(table:8**)

Dissolution Testing

was performed using a USP apparatus fitted with paddles (50 RPM) at 37^{o}C using Acetate buffer (pH4.0) as dissolution media. At a predetermined time interval (10minute); 10ml samples were withdrawn, filtered through 0.45µm PVDF filter, from that only 5ml was taken & diluted to 10ml with pH 4.0 acetate buffer and assayed at 217nm using UV visible Spectrometer. Shown 99% - 100% release **(table: 9**)

Wetting time:

Wetting time of the ODT is another important parameter, with the help of which we can assess the disintegration properties of the tablets. Wetting time of dosage form is related with the contact angle. A conventional method was used to measure the wetting time as well as capillarity of the orodispersible tablets. Five circular tissue papers of diameter 5.5cm are placed in a petridish with diameter 5.5cm. Ten ml of water containing Eosin, a water soluble dye, is added to petridish at room temperature. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of tablet is noted as wetting time. This wetting time detects the action of saliva in contact with the tablet. To illustrate the water uptake & the subsequent wetting of tablet Eosin dye was added to the water.All formulations found within10 seconds

Capping and Lamination tendency:

Due to the poor compaction property of the selected drug, the tablets were also examined for capping and lamination.Tablets were assessed visually for capping by observation of the final tablets for horizontal striation. Determination was made immediately after compression, immediately after friability testing and after 24 hours. The tablets were signs depending on their capping and lamination tendency

No capping (-), Low capping (+), High Capping (++), Very high Capping (+++).

Bitterness Index

Arbitrary bitter level index was needed to be developed. A numerical value was assigned to various level of bitterness as given in the Table below.

Table:3 Bitter Index Level

Numerical value	Scale
3.0	Strong bitter
2.5	Moderate to strong
2.0	Slight to moderate
1.5	Slight
1.0	Very slight
0	Taste less

This bitter level Index was used further in the study for the taste evaluation of the formulations. Along with bitterness test, certain other test are also highly essential for oral /Fast / rapid disintegrating tablets.

Result & Discussion:

From the dissolution profile of these above 3 batches i.e. [B5 (i), (ii), (iii)] it was concluded that the batch B5 (ii), in which the drug was complexed with β-Cyclodextrin in the ratio (1:1.5) shows 100% drug release within 60 minutes & it releases above 90% drug within 10 minutes. So in comparison to other batches the batch B5 (ii) shows better bioavailability.It"s hardness,friability ,disintegration time are also have optimum resuits **(table:23)** So this batch was used for further study.

From the above results it was concluded that Batch B6 (i) shows good disintegration time at maximum compression force, but in case of friability consideration it was exceeding 1.0%.Also in this batch where MCC(ceolus KG 802) was used as a filler produces unacceptable mouth feel. Batch B6(ii) Xylitol based ODT preparation shows good disintegration times .but only at lowest compression force, with increase in the compression force ,the tablet disintegration performance gets worse. So ODT with Xylitol as a filler only possible when lowest compression force was applied, so that the required disintegration time was achieved. For this formulation it is possible to evidence high increase of the disintegration time as a function of low increase of the compression force, but this condition is incompatible with large scale industrial tablet production.Batch B6(iii) Mannitol based ODT formulation shows good disintegration time at different compression forces, but in this case friability was exceeding 1% which was a major limitation.Batch B6 (iv) The combination of MCC (ceolus KG 802) & xylitol as a filler shows best disintegration characteristics i.e. good disintegration times at all compression forces, simultaneously at moderate to high compression forces the tablets of these batches shows acceptable friability. These results also demonstrate that MCC (Ceolus KG802) & xylitol based ODT shows most of the desired properties i.e. Good mouth feel, Sufficient hardness, Low friability, Rapid disintegration time. So the combination of MCC (Ceolus KG 802) & Xylitol based (as filler) ODT produces an interesting prototype for industrial scaling-up. Results of evaluation parameters are shown in **Table-4**.

Table:4 Evaluation parameter for ARP- BCD Complex

Batch code	Hardness(kp)	Friability (%)	D.T(sec)
B5(i)(1:1)	5-6	0.92	80
B5(ii)(1:1.5)	5-6	0.97	80-90
B5(iii)(1:2)	5-6	0.85	100

B5 (ii) Table : 5

Dissolution profile of Batch No-ARP-BCD ODT-B5(ii) (1:1.5)Complex

STD abs	0.598	0.598	0.598
Factor	99	99	99

DISSOLUTION PROFILE OF BATCH NO-Arp-ODT-B5(ii)(ARP(micro):Bcd(1:1.5)complexation										
TIME	ABSORBANCE			%RELEASE			AVG.	MIN.	MAX.	%RSD
	UNIT-01	UNIT-02	UNIT-03	UNIT-01	UNIT-02	UNIT03				
0	0	0	0	0	0	0	0	0	0	0
10	0.567	0.582	0.57	93.87	96.35	94.36	94.86	93.87	96.35	1.31
20	0.578	0.603	0.595	95.69	99.83	98.50	98.01	95.69	99.83	2.11
30	0.595	0.592	0.597	98.50	98.01	98.83	98.45	98.01	98.83	0.42
45	0.604	0.598	0.602	99.99	99.00	99.66	99.55	99.00	99.99	0.38
60	0.609	0.604	0.612	100.82	99.99	101.32	100.71	99.99	101.32	0.28

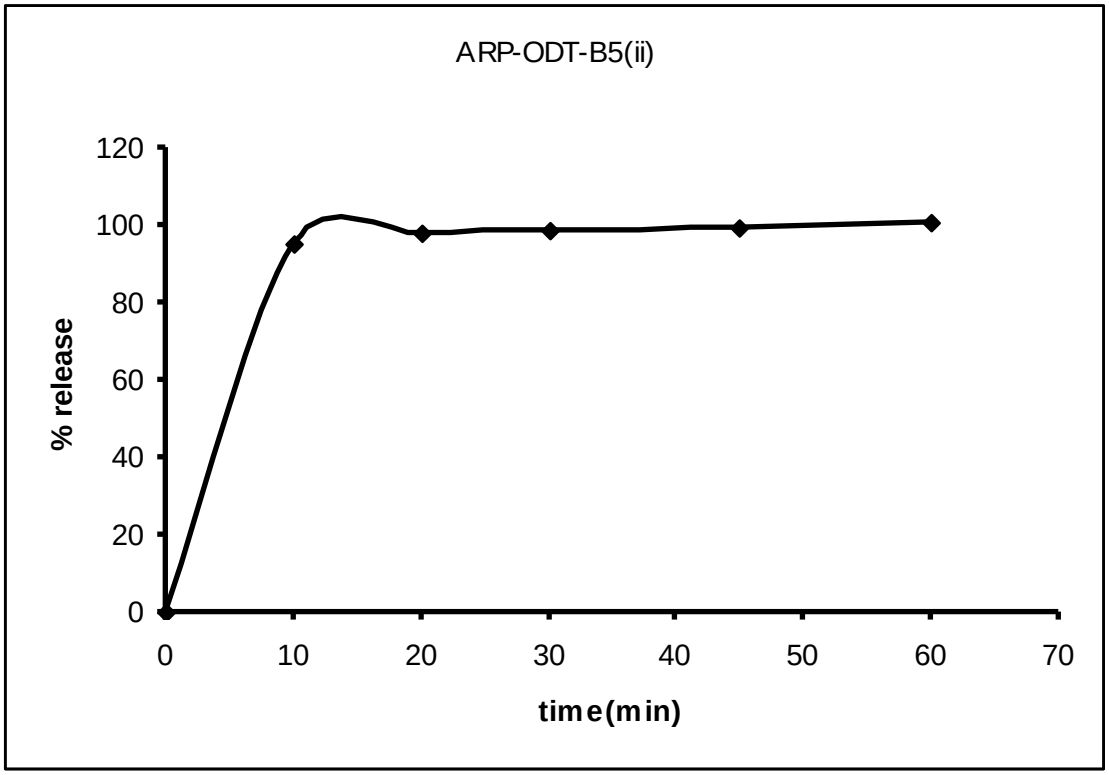


Fig :3 Zero order release for ODT B5(ii)

Table-6 Evaluation parameters of four ODT B6 (i) B6(ii) B6(iii) B6(iv) formulations

Batch code	Crushing strength(Kp)	Friability (%)	Disintegration Time(sec)
B 6 (i)	6-7	1.02	40
B 6(ii)	6-7	1.20	120
B 6(iii)	6-7	1.08	55
B 6(iv)	6-7	0.6	30

From the study of above table **B5(ii) (1:1.5)Complex** it can be concluded that increase in concentration of either of the independent variable e.g **% of Superdisinegrant and % of PVP as a binder and** crushing strength, percentage friability, & disintegration time were selected as dependent variables. plays an important role in disintegration time but the concentration of superdisintegrant causes more pronounced effect on the disintegration time rather the binder concentration factor is more marked as produces a significant impact on crushing strength.So to the optimized batch of **B 6(iv)** Acesulfame potassiumm,artificial sweetner, vanilla flavourwas added, 1% in batch X2 and 2 % in batch X3 whereas X1 is without it. using sweetener and flavours:shown in **Table:8, to mask the intensity of bitterness.**

.Table-7 Evaluation parameters of B 6(iv) Formulation

Parameters	Observed Values	Predicted values
Crushing strength	4.5	4.525
% Friability	0.79	0.803
Disintegration time (Sec)	45	44

Observed table concluded that the combinations gave the optimized results that were acceptable from the view point of crushing strength, friability, and disintegration time and 100% dissolution profile proceed further.

Table-8 Formulation of Taste masked tablets using sweetener and flavours

Formulation(gm)	BatchX1	BatchX2	BatchX3
ARP-BCD complex	12.5	12.5	12.5
MCC(Ceolus KG-802)	35.75	34.5	33.75
Xylitol	14.0	14.0	14.0
PVP k30	3.0	3.0	3.0
Mg.silicate	5.0	5.0	5.0
Crosspovidone	5.0	5.0	5.0
Acesulfame k+	-	0.75	1.5
Vanilla flavor	-	0.5	0.5
Aerosil	0.35	0.35	0.35
Iron oxide(red)	0.007	0.007	0.007
Magnesium stearate	0.064	0.064	0.064
IPA	q.s	q.s	q.s

The intensity of the bitterness was found out by comparing the bitter index level of the above 3 batches i.e. X1, X2, and X3 values shown in **Table:7**

Table:7 Evaluation test of final tablet formulations

Characteristics of the tablets			
Parameters	**Batch X1**	**Batch X2**	**Batch X3**
Crushing strength	6-7kP	5-6kP	5-6kP
% Friability	0.78	0.58	0.42
Disintegration Time	60sec	45sec	40sec
In vivo disintegration time	55 sec	43 sec	40sec
Bitterness Index	2	1	0

From the above table it was concluded that the batch X1 which is without any flavouring & sweetening agent having slight to moderate bitter index level, because in the optimized batch the drug was complexed with β-Cyclodextrin ,so its bitter taste was masked upto a certain extent. Batch X2 to which 1% of sweetening & flavouring agent was added & it was having slightly bitter index level, but the batch X3 with 2% sweetening & flavouring agent produces tasteless tablets with good & pleasant mouthfeel.So it was concluded that by means of addition of 2% of sweetening & flavouring agent the bitter taste masking was achieved upto the required level

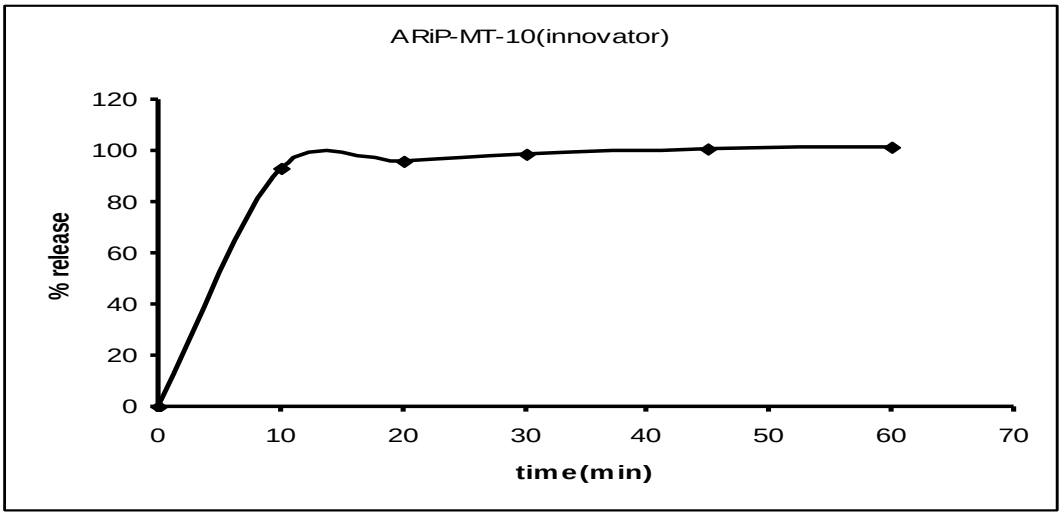
Table-10

Dissolution profile of B 6(iv) Formulation

STD abs	0.598	0.598	0.598
Factor	99	99	99

DISSOLUTION PROFILE OF B 6(iv) Formulation										
TIME	ABSORBANCE			%RELEASE			AVg.	MIN.	MAX.	%RSD
	UNIT -01	UNIT-02	UNIT-03	UNIT-01	UNIT-02	UNIT03				
0	0	0	0	0	0	0	0	0	0	0
10	0.561	0.556	0.568	92.87	92.05	94.03	92.98	92.05	94.03	1.00
20	0.572	0.578	0.581	94.70	95.69	96.19	95.52	94.70	96.19	0.86
30	0.588	0.601	0.595	97.34	99.50	98.50	98.45	97.34	99.50	0.72
45	0.602	0.605	0.612	99.66	100.16	101.32	100.38	99.66	101.32	0.55
60	0.609	0.612	0.618	100.82	101.32	102.31	101.48	100.82	102.31	0.48

Fig :3 Zero order release for ODT B6(iv)



CONCLUSION:

The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate & amount to elicit the desired pharmacological response. The rate or rapidity with which a drug is absorbed is an important consideration in the treatment of acute condition like asthma.epilepsy,cardiac failure.pain.etc.Solubility of drug can be enhanced by various technique ,but complexation with BCDis most commonly used .In this research work the solubility of ARP can be enhanced to the desired level by complexing it with BCDin a ratio of 1:1.5 & it was expected that cyclodextrin enhances overall absorption by influencing the dissolution kinetics.BCD is best suited for solubility enhancement of low dose drug. With low to moderate BCD: drug ratio it increases the solubility as well as absorption significantly, but with slightly increase in BCD: drug ratio decreases the dissolution kinetics & or bioavailability because a higher % bound drug limits the free drug in solution available for absorption.

The basic approach beyond the formulation of all ODTs is to maximize the porous structure of the tablet matrix & incorporating superdisintegrants at optimum concentration so as to achieve the rapid disintegration & instantaneous dissolution kinetics of the tablet. In this work the rapid disintegration of the tablet achieved by using 15 % of magnesium silicate & crosspovidone.Magesiumj.silicate is a novel superdisintegrant in the concentration range of 10 to 30 % it provides better disintegration properties of the tablet. During the formulation of ODTs selection of filler as an important criteria because of high friability & low resistence of the dosage form. It was found that Xylitol in combination with MCC (ceolus KG802) working as agood filler for ODT which provides good mouth feel, sufficient hardness, quicker disintegration & low friability. Finally the taste masking of the prepared ODT was achieved by using 2% of acesulfame K+ (as a sweetening agent) & vanilla flavor.

ARP-Aripiperazole
BCD-beta cyclo dextrin
MCC-microcrystalline cellulose
ARP-BCD – Aripiperazole and beta cyclo dextrin complex
ODTs-Oral dispersible tablets

FUTURE PROSPECTS:

Over the last decade, ODTs have grown steadily in demand & importance as aconvinient, potentially safer alternative to conventional tablets & capsules.ODTs are more popular because of its greater patient compliance. With the rapid acceptance of ODTs by patient & pharmaceutical companies, the market for the dosage form is promising & the product pipeline continuous to grow rapidly.ODTs offer life-cycle management opportunities for pharmaceutical marketers. In contrast with other technologies, such as modified release & microencapsulation, ODT will continue to provide enhanced therapeutic& commercial benefits. The main future challenge for ODT manufacturer includes reducing costs by finding ways to manufacture with conventional equipments, using versatile packaging, & improving mechanical strength & taste masking capabilities. Arbitrary bitter level index was needed to be developed.

REFERENCES:

1. Murray RM, et. Al. (1991). "The incidence of operationally defined schizophrenia in Camber well 1965–84". *British Journal of Psychiatry* 159: 790–794. Doi: 10.1192/bjp.159.6.790 (inactive 2008-07-05). PMID 1790446. Retrieved on 2008-07-05.
2. Somers JM, et.al.. (2002). "Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature". *Canadian Journal of Psychiatry* **47** (9): 833–43. PMID 12500753. Retrieved on 2008-07-05.
3. Sims A (2002). *Symptoms in the mind: an introduction to descriptive psychopathology*. Philadelphia: W. B. Saunders. ISBN 0-7020-2627-1.
4. Remington Volume-1
5. American Psychiatric Association (2000). "Schizophrenia", *Diagnostic and statistical manual of mental disorders: DSM-IV*. Washington, DC: American Psychiatric Publishing, Inc... ISBN 0-89042-024-6. Retrieved on 2008-07-04.
6. Scientific discussion –page 1 0f 29, (c) EMEA-2005.
7. Scientific discussion –page 2 0f 29, (c) EMEA-2005.
8. Rx only page 1 0f41.
9. Rx only page 1 0f41

10. US Food and Drug Administration, *CDER Data Standards Manual*, 2003, http:// http://www.fda.gov/cder/dsm/DRG/drg00201.htm, accessed March 19, 2005.
11. European Directorate for the Quality of Medicines, *Pharmeuropa*, **10** (4), 547 (1988), http:// http://www.pheur.org/, accessed March 19, 2005
12. K. Deepak, "Orally Disintegrating Tablets," *Tablets and Capsules* **7** , 30–35 (2004).
13. T.K. Ghosh *et al.*, "Quick Dissolving Oral Dosage Forms: Scientific and Regulatory Considerations from a Clinical Pharmacology and Biopharmaceuticals Perspective," in *Drug Delivery to the Oral Cavity: Molecules to Market*, T.K. Ghosh and W.R. Pfister, Eds. (CRC Press, New York, NY, 2005), pp. 337–356.
14. FDA, *Electronic Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations Current Through February 2005*, http:// http://www.fda.gov/cder/ob/default.htm, accessed March 18, 2005.
15. Orally disintegrating tablets Oct 2, 2005
    By: William R. Pfister, Tapash Oct 2, 2005
    Pharmaceutical Technology
    K. Ghosh
    Pharmaceutical Technology
16. Freeze drying technologies
17. Luca Dobetti, “Fast-Melting Tablets: Developments and Technologies “Pharma. Technol. Eur., 12 (9), pg 32-42 ; 2000.
18. Kaushik D., Dureja H., Saini T.R. ‘’Mouth Dissolving Tablets : A REVIEW ‘’ Indian Drugs 41(4) , Pg 187-193 ;April 2004
19. Roser B.J and Blair.: Rapidly soluble oral solid dosage form, methods of making same, and compositions thereof, US patent 5,762,961; 1998
20. Makino T., Yamada M and Kikuta J.; Fast dissolving tablet and its production , US patent 5,720,974 ; 1998
21. Koizumi K., Watanabe Y., Morita K., Utoguchi N, and Matsumoto M,; “ new method of preparating high porosity rapidly saliva soluble compressed tablet using mannitol with camphor, a subliming material, Int J. Pharm., 152, Pg 127 -131 ; 1997
22. Leon Lachmann, Herbert A. Lieberman, Joseph L. Kanig, ; The Theory and practice of industrial pharmacy, Third edition, Pg 328

23. C. Caramella et al., " Disintegrants in solid Dosage forms " Drug Dev. Ind. Pharm. 16 (17) , 2561-2577 ; 1990
24. Heinemann H. and Rothe W.: Preparation of porous tablets ; US patent 3,885,026 ; 1975
25. Allen L.V. and Wang B., Process for making a particulate support matrix for making rapidly dissolving tablet., US patent 5,587,180,; 1996
26. Allen L.V. and Wang B and Davies J. D., Rapidly dissolving Tablet., US patent 5,776,491; 1998
27. Gilis, Paul Marie Victor; De Conde, Valentin Florent Victor, "Fast-dissolving galanthamine hydrobromide tablet", *United States Patent,* 6,099,863, 2000.
28. Bi, Y. et al., " Preparation and Evaluation of a Compressed Tablet Rapidly Disintegrating in the Oral Cavity", *Chem. Pharm. Bull***.**, 1996, 44 (11), 2121-2127.
29. Wantanabe, Y. et al., " New Compressed Tablet Rapidly Disintegrating in the Mouth using Crystalline Cellulose and a Disintegrant", *Biol. Pharm. Bull.,* 1995, 18 (9), 1308-1310.
30. Mane Avinash R, Kusum devi V and Asha AN. "A novel technique for preparation of mouth dissolving tablets of Domperidone" *Indian drugs,* 2003; 40(9), 544-6.
31. Koizumi K., Watanabe Y., Morita K., Utoguchi N, and Matsumoto M,; " new method of preparating high porosity rapidly saliva soluble compressed tablet using mannitol with camphor, a subliming material, Int J. Pharm., 152, Pg 127 -131 ; 1997
32. Makino T., Yamada M and Kikuta J.; Fast dissolving tablet and its production , US patent 5,720,974 ; 1998
33. Rajan K. Verma & Sanjay Garg " Drug delivery technologies and future directions" Pharm. Technol. 25 (2), pg 1-14 ; 2001
34. Cherukuri S. R. et al " Process for forming quickly dispersing comestible unit and product therefore" US patent 5,587,172 ; 1996

35. G.L. Myers, G. E Battist & R. C. Fuisz " Process and apparatus for making rapidly dissolving dosage unit and product therefore " PCT Patent WO 95/ 34293-A1 ; 1995
36. G Cousin ; E Bruna, and E. Gendrof " Rapidly disintegrating multiparticulate tablet" US patent 5,464,632.; 1995.
37. Wehling , F. et al " pediatric effervescent dosage form US Patents 5,223,264 ; 1993
38. Takao M., et al, " Intrabuccally dissolving compressed moulding and production process thereof US patent 5,576,014 ; 1996
39. Gregory G. K. E et al., " Articles for carrying chemicals " US patent 4,371,516 ; 1983
40. Gregory G. K. E et al., " Pharmaceutical dosage form packages " US patent 4,305,502.; 1981
41. http://www.kvpharma.com/tech/3_1_oraquick.html, Accessed on April ' 05
42. Laboratoire Lafon , " Galenic Form for oral administration and its method of preparation by lyophilization of an oil-in- Water Emulsion," European patent 0,159,237.; 1985
43. D.J. Gole et al., "Preparation of pharmaceutical and other matrix system by solid – state dissolution", US patent 5,215,756. , 1993
44.

1. Chandrasekhar an NV *et. al*., COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression, Proc. Natl. Acad. Sci. USA, 99, 13926-13931;2002
2. www.medicinescomple.com; Sweetman S (Ed), Martindale: The complete drug reference. London: Pharmaceutical Press. Electronic version, 2005.
3. www.indiamediworld.com; Indian Drug Review, Issue : Jan – Feb 2005, Accesed on 12 Feb'05
4. Sastry, S.V. et al., Atenolol Gastrointestinal Therapeutic System I Screening of formulation variables. , Drug. Dev. Ind. Pharm., 23, 157-165, 1997

5. Fasano, A. Novel approaches in oral delivery of macromolecules. J. Pharm. Sci. 1351- 1356, 1998
6. Indurwade N.H et al., Fast dissolving tablets , Indian Drug, Pg 405, Vol.39 (8) , 2002
7. Dr M. C. Gohel, Garima Bansal, Nayna Bhatt "Formulation and Evaluation of orodispersible Taste Masked Tablets Of Famotidine." Pharma Bio World; Vol 3 ,(5); March-April 2005
8. Bhusan S. Y., Sambhaji S. P., Anant R.P. and KakasahebR.M.: New drug delivery system for elderly, Indian Drugs, 37, pg 312-318; 2000.
9. Luca Dobetti, "Fast-Melting Tablets: Developments and Technologies "Pharma. Technol. Eur., 12 (9), pg 32-42 ; 2000
10. Maarschalk, K. V. V. and Bolhuis, G. K., Pharm. Technol. Eur., 10, pg 28 ; 1998
11. www.pheur.org; European Directorate for the Quality of Medicines, Pharmeuropa 10 (4), 547, 1998 Accessed on Jan'05
12. Srikonda Venkateswara Sastry, Janaki Ram Nyshadham and Joseph A. Fix; "Recent technological advances in oral drug delivery – a review"; PSTT Vol. 3, NO. 4; Pg 138- 144, April 2000.
13. Robin H. Bogner, Meghan F. Wilkosz, "Fast-Dissolving Tablets" www.uspharmacist.com ; Accessed on feb '05
14. Wilson, C.G. , The behaviour of a fast dissolving dosage form (Expider) followed by gamma- Scintigraphy , Int. J. Pharm 40, Pg 119 – 123 ; 1987
15. Chang RK, Guo X, Burnside B, Couch R. Fast-Dissolving Tablets, Pharm Technol; 24(6):52-58.; 2000
16. Vanscoik K.G.: Solid pharmaceutical dosage in tablet triturate form and method of producing same, U.S. patent ,5,082,667., 1992
17. Pebley W.S., Jager N.E. and Thompson S.J.: Rapidly disintegrating tablet, U.S. Patent, 5,298,261., 1994
18. Kaushik D., Dureja H., Saini T.R. ''Mouth Dissolving Tablets : A REVIEW '' Indian Drugs 41(4) , Pg 187-193 ;April 2004
19. Seager H. Drug-deliver Products and the Zydis Fast-dissolving Dosage Form. J Pharm and Pharmacol; 50:375-382.; 1998

20. R. Yarwood," Zydis – A novel, Fast Dissolving Dosage Form," Man. Chem. 36 – 37 ; Feb, 1990
21. Roser B.J and Blair.: Rapidly soluble oral solid dosage form, methods of making same, and compositions thereof, US patent 5,762,961; 1998
22. Heinemann H. and Rothe W.: Preparation of porous tablets ; US patent 3,885,026 ; 1975
23. Kinitsch K., Hagen A., Munz E. and Determenn H,; Production of porous tablets, US patent 4,134,943 ; 1979.
24. Irwin C.J. , Norbert S.M. and Robert E.S.; Method of producing tablets with improved dissolution properties, European patent US 2002136767, 2002
25. Koizumi K., Watanabe Y., Morita K., Utoguchi N, and Matsumoto M,; " new method of preparating high porosity rapidly saliva soluble compressed tablet using mannitol with camphor, a subliming material, Int J. Pharm., 152, Pg 127 - 131 ; 1997
26. Makino T., Yamada M and Kikuta J.; Fast dissolving tablet and its production , US patent 5,720,974 ; 1998
27. Leon Lachmann, Herbert A. Lieberman, Joseph L. Kanig, ; The Theory and practice of industrial pharmacy, Third edition, Pg 328.
28. C. Caramella et al., " Disintegrants in solid Dosage forms " Drug Dev. Ind. Pharm. 16 (17) , 2561-2577 ; 1990
29. Allen L.V. and Wang B., Process for making a particulate support matrix for making rapidly dissolving tablet., US patent 5,587,180,; 1996
30. Allen L.V. and Wang B and Davies J. D., Rapidly dissolving Tablet., US patent 5,776,491; 1998
31. Rajan K. Verma & Sanjay Garg " Drug delivery technologies and future directions" Pharm. Technol. 25 (2), pg 1-14 ; 2001
32. Cherukuri S. R. et al " Process for forming quickly dispersing comestible unit and product therefore" US patent 5,587,172 ; 1996
33. G Cousin ; E Bruna, and E. Gendrof " Rapidly disintegrating multiparticulate tablet" US patent 5,464,632.; 1995

34. G.L. Myers, G. E Battist & R. C. Fuisz " Process and apparatus for making rapidly dissolving dosage unit and product therefore " PCT Patent WO 95/ 34293-A1 ; 1995
35. Wehling , F. et al " pediatric effervescent dosage form US Patents 5,223,264 ; 1993
36. Wehling F, et al, Effervescent dosage form with microparticles, US patent 5,178,878. ; 1993
37. Takao M., et al, " Intrabuccally dissolving compressed moulding and production process thereof US patent 5,576,014 ; 1996
38. Gregory G. K. E et al., " Articles for carrying chemicals " US patent 4,371,516 ; 1983
39. Gregory G.K. E " Solid shaped article "US patent 4,758,598 ; 1988
40. Gregory G. K. E et al., " Pharmaceutical dosage form packages " US patent 4,305,502.; 1981
41. http://www.kvpharma.com/tech/3_1_oraquick.html, Accessed on April ' 05
42. Laboratoire Lafon , " Galenic Form for oral administration and its method of preparation by lyophilization of an oil-in- Water Emulsion," European patent 0,159,237.; 1985
43. D.J. Gole et al., "Preparation of pharmaceutical and other matrix system by solid –state dissolution", US patent 5,215,756. , 1993
44. Analytical profiles of drug substances., Vol -14 Klaus Florey pg, 551
45. Clarke's Analysis of Drugs and Poisons, London: Pharmaceutical Press. Electronic version, 2004
46. Indian Pharmacopoeia, Controller of Publication , New Delhi VOl- II, Pg 555-556 ,1996
47. United States Pharmacopoeia 24 NF 19 , Asian edition United states Pharmacopoeial Convention ,Inc., Rockville, MD , 457 -460,1842
48. British Pharmacopoeia, HMSO Publication London , VOl. II Pg 1046 ; 2002
49. European Pharmacopoeia , 3rd Edition; Pg1487-1488,1288-1289; 1997
50. Japanese Pharmacopoeia ,13th Edition; Pg 328-329 ;183-184 1996
51. Pharmacology by Hãf Rang, M.M. Dale and J.M. Ritter, Fourth Edition , Pg 230-237

52. Hardman, Joel G., Limbird, Lee E.; " Goodman & Gilman's , The Pharmacological basis of therapeutics", 10th Edition ; 2001, Pg 688
53. www.rxcipient.com, accessed on Feb ' 2005
54. www.medicinescomple.com " Hand book of Excipients" accessed on April ' 2005
55. www.dekker.com;Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches, Drug dev.Ind.Pharm, 2004, Accesed on march -2005
56. Kornblum, J. Preparation of rapidly disintegrating compressed tablets ", US patent 5,145,554. , 1993
57. Ponchel , G. Duchene, D, Drug Dev. Ind. Pharm., 16 (4) : 613, 1990
58. Yuxia, Bi, Sunada H, Drug Dev. Ind. Pharm 25 (4) , 571, 1999
59. Ito A. and Sugihara M.,: Development of oral dosage form for elderly patient: Use of agar as base of rapidly disintegrating oral tablets, Chem. Pharm. Bull., 44, 2132-2136 ; 1996.
60. Watanabe Y., Ishikawa Y., Utoguchi N., and Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter masked granules by the compression method, Chem . Pharm. Bull. 47, 1451-1454, 1999.
61. Ishikawa Y., Kuizumi N. , Mukai B., Utoguchi N., Fuji M., Matsumoto M., Endo H., Shirrotake S., and Watanabe Y. :m Preparation of rapidly disintegrating tablet using new type of Microcrystalline cellulose (PH-M series) and L- HPC by direct compression method., Chem. Pharm. Bull.49., 134 – 139., 2001
62. Makooi – Morehead W. T., Buehler J. D. and Landmann B. R. : Formulation of fast dissolving efavirenz capsules or tablets using Super disintegrants , US patent 6,238,659., 2001.
63. Gillis P.M.V. and Deconde V.F.V. .: Fast dissolving tablets of galanthamine hydrobromide tablets US Patent 6,009,863., 2000
64. Shimizu , Toshihiro, Sugaya, Masage, PCT Int Appl WO 98 53, 7918 , through Chem Abst., 130 (11) " 1128, 44194s (1999)
65. Shaibahara Sadaichi, Masuda, Kiyoshi, HGirooka Yukio, Nakatani, Jp 2000119 , 175 ; Through Chem Abst 132 (20) 270108w , 2000.

66. Itoh, A. and Niwas, T. PCT Int Appl WO 9830, 209 , through Chem Abst., 129 (10) " (1998)
67. Dobetti Luca, PCT Int Appl WO 9838, 496 , through Chem Abst., 131 (14) " 1166,189736 ;(1999)
68. Santus, G., Golzi, R., Lazzarini, C., Marcelloni, L., PCT Int Appl 09947,172; Through Chem Abst., 131 (18) " 2482434,;(1999)
69. Ishikawa T., Mukai B.,Shiraishi S., Utoguchi N., Fujii M., Matsumoto M., Watanabe Y., "Studies of Rapidly Disintegrating Tablet Prepared by Direct Compression Method," Part IV: *Chem. Pharm. Bull*., **49**, 134—139 (2001).
70. Naji Najib and Ibrahim Jalal "Correlation between dissolution and disintegration rate constants for acetaminophen tablets" Powder Technology Volume 34, Issue 1 , Pages 39-51,January-February 1983.
71. Chauveau, C., Gendrot , E., Demichelis , A.G. Nouri, N., PCT Int Appl. WO 9904,763
72. Ream, Roland L.; Wokas, William J. " Flavoured product containing medicament or other active agent and a masking agent such as saccharides" US patent 9,478,17 , April 2001
73. Oury ; Pascal; Lamouxrex; Gael, Herrry; Catherine; Prevost " Multilayer Orodispersible Tablet" US Patent Appl Publ. US 247,677; 2004
74. Kim , Hyun Soo; Park, Young Joon; Kang, Dae Sik, US Patent No. 71,864 , 2002
75. Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle P "The preparation of orally disintegrating tablets using a hydrophilic waxy binder." Int J Pharm.;294(1-2):1-10 ; 2005 Apr 27.
76. Augello M.,Dell S., M. ReierG. E., Stamato H. J., Di Memmo L. M., " Crosscarmellose Taste Masking; U S Patent, 6,099,865 ; Aug 2000.
77. Terashita K., Imamurak, " Preparation of antipyretic analgesic by direct compression" Chem Pharm Bull (Tokyo), 50 (12) Pg- 1542-1549, Dec 2002
78. Hunter; Edward A. (Glenham, NY); Zeleznik; Joseph A. (New Paltz, NY); Sherwood; Bob E. (Amenia, NY) "Directly compressible high load

acetaminophen formulations" United States Patent: 5,965,166November 5, 1997

79. Haisa, M.; Kashino,S; Maeda, H. The Orthorhombic form of p-Hydroxyacetanilide. Acta Crystallogr. (30) ; Pg 2510-2512 ; 1974
80. Di Martino, P.; Conflant, P; Drache, M; Huvenne, J.P; Guyout- Hermann, A-M; "Preparation and physical characterization of Form II and III of Paracetamol", J. Therm. Anal. 48, Pg 447-458; 1997.
81. Joiris E., Di Martino P., Berneron C, Guyot Hevmann AM, Guyou J. C. "Compression behaviour of orthorhombic paracetamol" Pharma Res . 15(7); Pg 1122-1130.; Jul 1998
82. Espeau P, ceotin R, Tamarit JL, Perrin MA, Gauchi JP, Leveiller F "Polymorphism of Paracetamol: Relative stabilities of the monoclinic and orthorhombic phases inferred from topological pressure temperature and temperature volume phase diagram" J Pharm. Sci., 94(3) 54-39; Mar. 2005.
83. Garekani HA, FordJL, Rabistein MH, Raja bi siahboomi AR "Highly Compressible paracetamol: I - Crystallization and characterization" Int. J. Pharm 208 (1-2) pg 87 – 99; Nov 2000.
84. Garekani HA, Ford JL, Rubinstein MH, Rajabi siahboomi AR "Highly Compressible paracetamol: II - Compression Properties" Int. J. Pharm 208 (1-2) pg 101 – 110; 2000.
85. Garekani HA, Ford JL, Rubinstein MH, Rajabi siahboomi AR "Formation and Compression characteristics of prismaticpolyhedral and thin plate-like Crystals of paracetamol" Int. J. Pharm 187(1)) pg 77 – 89; Sep-1999.
86. Rasenack N Muller BW, "Crystal habit and tableting behavior." : Int J Pharm.;244(1-2):45-57. ; Sep 2002
87. J. -M. Fachaux, A. -M. Guyot-Hermann, J. -C. Guyot' P. Conflant, M. Drache, S. Veesler and R. Boistelle, "Pure Paracetamol for direct compression Part I. Development of sintered-like crystals of Paracetamol" Powder Technology Volume 82, Issue 2 , Pages 129-133; Feb 1995.
88. J. -M. Fachaux, A. -M. Guyot-Hermann, J. -C. Guyot' P. Conflant, M. Drache, S. Veesler and R. Boistelle, Pure Paracetamol for direct compression Part II. Study

of the physicochemical and mechanical properties of sintered-like crystals of Paracetamol, Int J Pharm. Vol.81, Issues 2-3, Pg 187-192; Mar 1992,

89. Kachrimanis K. Malamataris S., "Cyrstallization of Paracetamol from ethanol-water solutions in the presence of polymers. J Pharm Pharmacol. 51(11) 1219-27; Nov 1999.
90. Alzoubi N., Malamataris S., "Effect of Initial concentration and seeding procedure on crystallization of orthorhombic paracetamol from ethanolic solution" Int J. Pharm. ;260(1), Pg 123-135. Jul 2003
91. AL Zoubi N, Nikolakakis I, Malamataris S "Crystallization condition & formation of orthorhombic paracetamol from ethanolic solution" J Pharm. Pharmacol. 54(3) 35-33; Mar. 2002
92. Simonelli, A. P., Mehta S. C, Higuchi, W. I. " Inhibition of sulphathiazole crystal growth by PVP , J. Pharm. Sci., 59 ; Pg 633-638 ; 1970.
93. www.pharmtech.com; Alebiowu G. and Itiola O. A. " Effect of natural and Pregelatinised sorghum, Plaintain, and Corn starch binders" Pharm. Tech.; Pg 26-30 , 2001
94. Salazar de Saavedra M. , Saavedra Cuadra, Application of a sensorial response model to the design of an oral liquid pharmaceutical dosage form, *Drug Dev. Ind. Pharm., 26* (1) , Pg 55–60. 2000
95. Gowan W., G. Bruce R., D. Aliphatic Esters as a Solventless Coating Pharmaceuticals US. Pat. Appl. CA2082137 November 4, 1993
96. Miura S., Matsushita M., Fujinaga T., Syrup Pharmaceutical US Patent 04,187,629 ;1992,
97. Morella A., M. Lucas S., Microcapsule Compositions and Process" US. Pat. Appl. CA2068366 , 1992
98. Roche E., J. Taste-Masking and Sustained-Release Coatings for Pharmaceuticals Eur. Pat. Appl. EP0459695 December 4, 1991
99. Toraishi K. , Nakamura N. , Yuizono Y. , Mori M. , Kurokawa M., Application of a rapid–jelly form confectionery for improving children's compliance in taking bitter medicines,.*Eur. J. Pharm.,Sci. 24* (5) , 479–483; (1988)

100. Blase C., M. Shah M., N. Taste-Masked Pharmaceutical Suspensions for Pharmaceutical Actives Eur. Pat. Appl. EP0556057 August 18, 1993
101. Lukas , Stefan PCT Int. Appl. WO 9739,747 through Chemical Abstract 127, 362628, 1997.
102. B. Albertini ; C. Cavallari, N. Passerini ; D. Voinovich ; M.I. Gonzalez Rodrigher, L. Magarotto & L. Rochiguez , « Characterization & taste masking evaluation of acetaminophen granules" Comparison between different preparation method in a high shear mixer; Eur,. J. Pharm. Sci. Vol-21 (2-3) pg – 295 -303 (2004)
103. Duru C, Boudeville P, Delalonde M, Farah N., Melt granulation with glyceryl palmitostearate to obtain taste-masked acetaminophen, Acta. Pharm. 62 (3) pg 186 -192, May 2004
104. Corbo M., Desai J., Patell M., Warrick R., Taste Masking Coating Composition US Patent 6,551,617 April 22, 2003
105. Suzuki H. , Onishi H. , Hisamatsu S, Masuda K., Takahashi Y. , Iwata M. , Machida Y., Acetaminophen – Containing chewable tablets with suppressed bitterness and improved oral feeling. Int J Pharm. 278 (1) Pg 51-61 , 18 Jun 2004.
106. Hoy M., R. Roche E., J. Taste Mask Coating for Preparation of Chewable Pharmaceutical Tablets Eur. Pat. Appl. EP0523847 January 20, 1993
107. Breitkreutz . J., Bornhoft M, Woll F, Kleinebudde P. " Pediatric drug formulation of sodium benzoate : I Coated granules with a hydrophilic binder. Eur J. Pharm Biopharm. 56(2), pg 247-253, Sep 2003
108. Nouri N., Zuccarelli J., M. Chauveau C., Bruna E., Process for Manufacturing Coated Granules with Masked Taste and Immediate Release of¼{he Active Principle US Patent 6,660,382 December 9, 2003.

	A	B	C	D	E	F	G	H	I
Crushing strength	5.5	6	7.2	4..5	5	6	4.5	4	4.2
%Friability	1.12	1.07	0.87	1.02	0.82	0.61	0.79	0.81	0.52
Disintegration time	180	240	300	120	150	170	45	60	100

Formulation(gm)	**BatchX1**	**BatchX2**	**BatchX3**
ARP:β-CD complex	12.5	12.5	12.5
MCC(Ceolus KG-802)	35.75	34.5	33.75
Xylitol	14.0	14.0	14.0
PVP k30	3.0	3.0	3.0
Mg.silicate	5.0	5.0	5.0
Crosspovidone	5.0	5.0	5.0
Acesulfame k+	-	0.75	1.5
Vanilla flavor	-	0.5	0.5
Aerosil	0.35	0.35	0.35
Iron oxide(red)	0.007	0.007	0.007
Magnesium stearate	0.064	0.064	0.064
IPA	q.s	q.s	q.s