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FORMULATION AND OPTIMIZATION OF ORODISPERSIBLE TABLET OF INDOMETHACIN

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ABSTRACT

In the present study, Indomethacin is a nonsteroidal anti-inflammatory drug was chosen as model drug for formulation into pediatric orodispersible tablet. Design of experiment were based on 2^3 factorial design and total of eight batches of tablet was formulated. Highly porous tablet with acceptable mechanical strength were formulated by direct compression technique using a combination of sublimizing agent and superdisintegrant in the formulation. Camphor and ammonium bicarbonate were chosen as sublimating agents which were subjecting volatilization at 50^0C for 8hrs from the tablet matrix. Preliminary trial were carried out to study the effect of volatilizing agent on disintegration time and hardness of tablet, to study the effect of mode of incorporation of superdisintegrant, intragranular and/ or extragranular to study combined effect of volatilizing agent and superdisintegrant to optimize hardness. Wetting time, Water absorption ratio, Porosity drug content and In vitro drug release in phosphate buffer (pH 6.4 and pH 7.4) were investigated. Surface morphology of prepared orodispersible tablet was investigated by scanning photograph and SEM. The stability studies were carried out in accordance to ICH Q_1 A guideline for six month to investigate the influence of humidity and temperature on the crushing strength, disintegration time and drug content.

KEYWORDS: Orodispersible, Factorial Design, in Vitro Release, Stability Studies.

INTRODUCTION

Solid dosage forms enjoy popularity due to a variety of reasons viz. ease of administration, self medication, and pain avoidance as compared parenteral and are also economical. However, difficulty in swallowing is a common problem of all age groups, especially the geriatrics and pediatrics, because of physiological changes associated with these groups. Other categories that experience problem in using conventional oral dosage forms include the mentally ill, non-cooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing.

Swallowing of solid dosage forms like tablet and capsules and improper dosing of suspension and emulsion may produce difficulty for pediatrics due to incomplete development of muscular and nervous system. Sometimes it may be difficult to swallow conventional product due to unavailability of water. These problems can be solved by development of a novel type of solid oral dosage form namely mouth dissolving tablets, which disintegrate and dissolve rapidly in saliva without the need of drinking water. They are also known as orodispersible tablet, fast dissolving tablets, melt in mouth tablets, rapimelts, porous tablets, quick dissolving or rapidly disintegrating tablets. In these cases, the bioavailabilities of drugs are significantly greater than those observed from standard dosage form. The advantages of dispersible tablets are recognized by industry and patients, since there are several products available in the market.[1] A wide range of drugs such as narcoleptics, cardiovascular drugs, analgesics, antihistamines and drugs for erectile dysfunction and be considered as suitable candidates for this dosage form.[2] For rapid dissolution of the dosage forms, water must rapidly penetrate into the tablet matrix to cause quick disintegration an instantaneous dissolution of the tablet.[3] The advantages of orodispersible dosage forms are increasingly being recognized in both industry and academia.[4] their growing importance was underlined recently when European Pharmacopoeia adopted the term "Oral dispersible Tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.[5]

MATERIAL AND METHOD

Indomethacin was optained as a gift sample from M/S Siemen laboratories, Gurgaon, India. Polyplasdone XL® was purchased from Fine Chemicals Ltd, Gujrat, India.

All other chemicals and reagents used were of analytical grade.

INDOMETHACIN

(2-[1-(4-chlorobenzoyl)-5methoxy2methyl-indol-3-yl] acetic acid.[8]

is a drug used in musculoskeletal and joint disorders, including spondylitis, osteoarthritis, rheumatoid arthritis and acute gout. It is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached in about 2 hrs after a single dose. The terminal plasma half-life has been reported to be range 2.6 to 11.2 hrs. Indomethacin is used in management of inflammation and pain, as orodispersible tablets disintegrate within seconds thus quick onset of action can be achieved by formulating orodispersible tablets of indomethacin.

Preparation of orodispersible tablets: The 2^3 factorial designs were implemented for the optimization of pediatric indomethacin (orodispersible tablet.[9] The dependent response measured disintegration time and crushing strength. Three independent factor concentration of camphor, concentration of ammonium bicarbonate, concentration of mannitol were set at two differ levels.[10]

Table 1: Experimental Design 2^3 with higher and lower level of factor used to optimize the formulation.

Factor Combination	Camphor (%w/w)	Ammonium Bicarbonate (%w/w)	Mannitol (%w/w)
F_1	10	10	29
F_2	14	10	29
F_3	10	14	29
F_4	14	14	29
F_5	10	10	45
F_6	14	10	45
F_7	10	14	45
F_8	14	14	45

Before implementation of experimental design preliminary studies were carried out to study effect of various formulation variables on disintegration time and hardness of tablet to be prepared. Formulation F_8 was selected for the preliminary trails as it contained higher levels of camphor, ammonium bicarbonate and mannitol and thus produce higher response values for variables studied.

EFFECT OF VOLATILIZING AGENT ON DISINTEGRATION TIME AND HARDNESS OF TABLET

Formulation F_8 containing all ingredient as per the design, except the superdisintegrant was tableted. Both volatilizing agents were incorporated as 14% (w/w) of total formulation. The granules were prepared by non-aqueous granulation technique using 10% (w/w) PVP ethanolic solution as binder and passed through sieve no 10 and subjected to initial drying in hot air oven for period of 30 minute. The dry granules were passed through sieve no 22 and dried at 60°C for 1 hr. The granules were compressed to tablet by single punch tablet press. The prepared tablet was subjected to the evaluation parameter of disintegration time and hardness.

EFFECT OF MODE OF INCORPORATION OF SUPERDISINTEGRANT INTRAGRANULARY AND EXTRAGRANULARLY

F_8 was prepared containing all formulation ingredients except the volatilizing agent to study the effect of mode of addition of superdisintegrant Crosspovidone. For intragranular incorporation 4% (w/w) superdisintegrant was incorporated during formulation of granule and for extragranular incorporation 4%(w/w) superdisintegrant was incorporated after the formulation of granule and for both i.e. intragranular and extragranular 2%(w/w) superdisintegredient was incorporated during formulation of granule and 2%(w/w) was incorporated after formulation of granule.

COMBINED EFFECT OF VOLATILIZING AGENT AND SUPERDISINTEGRANT

In this study both super disintegrant and volatilizing agent were incorporated into F_8 as per the factorial design. The volatilizing agent were incorporated up to 14% (w/w) and super disintegrant 4% (w/w) [2%(w/w) intragranularly and 2% (w/w) extragranularly] granulated and compressed in tablet as discussed in earlier section.

OPTIMIZATION OF HARDNESS

Hardness of tablet of batch F8 was found low value thus an attempt was made to improve the hardness of tablet by incorporation of 1% (w/w) colloidal silicon dioxide.[11]

PREPERATION AND EVALUATION OF ORODISPERSIBLE TABLET[6]

The prepared orodispersible tablets were evaluated for disintegration time and hardness and optimum formulation characteristics were determined. The obtained data was used for selection of the level of sublimizing agent and mode of superdisintegrant incorporation in order to prepare the orodispersible tablet.[12] Accurately weighed quantity of indomethacin, sublimizing agent – camphor, ammonium bicarbonate, mannitol, intragranular fraction of POLYPLASDONE

XL® and other excipients were passed through the sieve number 10 and mixed in a glass mortar. The above blend was granulated by the non-aqueous granulating agent viz alcoholic solution of PVP (10% w/w) and passed through sieve number 18. The granule were air dried and were mixed with extragranular fraction of POLYPLASDONE XL®, 1% (w/w) colloidal silicon dioxide was incorporated and granules were passed through sieve no. 22, lubricated with magnesium stearate and compressed on single punch tablet press. The prepared tablet was subjected to volatilization at 50°C for 7 hrs until constant weight was achieved, to ensure complete sublimation of camphor and ammonium bicarbonate. The tablets were evaluated for crushing strength using Monsanto hardness tester, percentage drug content and disintegration time. The disintegration time of the orodispersible tablet was determined by employing a disintegration apparatus. 700ml of water maintained at 37°C±2 and rotate with rpm 28-32 cycle up down of basket. Disintegration time was recorded when all the fragments of disintegrated tablet passed through the screen no # 10 of the basket.[6]

SELECTION OF OPTIMIZED FORMULATION

The optimized formulation was selected based on the result obtained from evaluation parameter (Disintegration time, drug content, hardness). The formulation that showed a disintegration time less than 60sec desirable hardness and drug content with in pharmacopoeial limit was selected for further evaluation.

OPTIMIZATION OF VOLATILIZATION TIME

The residual levels of ammonium bicarbonate were analyzed quantitatively by titrimetric method and the residual level of camphor was analyzed qualitatively. For ammonium bicarbonate six tablets of F_5 and F_6 were subjected to temperature of 50°C in hot air oven for sublimation and kinetics data was generated by withdrawing samples at regular intervals of 1hr for a period of 6hr. The samples were crushed and back titration was carried to determine the equivalent factor. 1ml of 0.5M H_2SO_4 is equivalent to 79.1 mg of ammonium bicarbonate. Using potassium hydrogen phthalate, sodium hydroxide was standardized.

The % content of ammonium bicarbonate was calculated by

$$\frac{[(V_1 \times N_1) - (V_2 \times N_2) \times \text{Equivalent Factor} \times 100]}{W}$$

V_1- Volume of acid, N_1- Normality of acid, V2- Volume of alkali, N_2- Normality of alkali and
W- Weight of sample.

Kinetic plot of residual level of ammonium bicarbonate Vs time were made on Cartesian graph and sublimation rate and time required for zero % residual levels of ammonium bicarbonate determined.

And for determination of residual level of camphor, six tablets of F_5 and F_6 were subjected to temperature of 50°c in hot air oven for sublimation and kinetics data was generated by withdrawing samples at regular intervals of 1hr for a period of 6hr.

EVALUATION OF OPTIMIZED FORMULATION[13]

The F_5 and F_6 formulation (optimized formulation) were subjected to the different investigation like surface morphology, porosity, wetting time, water absorption ratio, in vitro disintegration test, In vitro drug release and stability studies.

SURFACE MORPHOLOGY

The surface morphology of tablet before and after volatilization of camphor and ammonium bicarbonate from tablet matrix, were studied by SEM photomicrograph. The tablet were sputter for 5 to 10 min with gold particle by using fine coat ion sputter and examined under SEM.

POROSITY

The porosity of tablet was calculated by using following formula

$\varepsilon_{\%} = (1-\delta_{ap}/\delta) \times 100$

ε% is the Percentage porosity, δ is True density and δ_{ap} is Apparent density calculated by using mean weight, diameter and thickness of tablet.[14]

WETTING TIME

Wetting time of tablet was measured by taking five circular tissue paper of 10cm diameter were placed in petridish of 10cm diameter.10ml of water containing methylene blue (0.1%w/v) was added to petridish. A tablet was carefully placed on the surface of tissue paper and time required for the dye to reach the upper surface of the tablet was recorded. The measurement was done in triplicate.

WATER ABSORPION RATIO

Five circular tissue paper of 10cm diameter were placed in petridish of 10cm diameter. 10ml of water containing methylene blue (0.1%w/v) was added to petridish. Preweighed tablet was carefully placed on the surface of tissue paper and reweighed after the water reached to the upper surface of tablet. Water absorption ratio was calculated by-

Water absorption ratio = $(W_b - W_a) / W_a$

W_a is the weight of tablet before absorption of water, W_b is weight of tablet after absorption of water.

INVITRO DISINTREGRATION TEST

In vitro disintegration time of selected formulation was evaluated by using modified dissolution apparatus. Kinetic digital image of disintegration behaviour were recorded by using digital camera. One tablet of formulation F_6 was placed in a glass full of water and the dispersion process was recorded.[6]

INVITRO DRUG RELEASE

The In vitro drug release from prepared orodispersible tablet and immediate release tablet of Indomethacin was studied using USP apparatus with paddle (100 rpm at 37^0C±0.5^oC). Dissolution were carried out in phosphate buffer 6.4 and 5ml sample were withdrawn at specific time interval, replaced with fresh media and analyzed at 319nm. Similarly another dissolution studies were carried out in Phosphate buffer 7.4.

STABILITY STUDIES

Stability studies were carried out as per ICH Q_1A stability testing guideline for zone III. The formulated orodispersible tablet was subjected to storage condition of 40^0C±2/75% RH±5 for 6 month in closed container. The sampling interval was 0, 1, 2, 3 and 6 months. The sample was evaluated Disintegration time, Crushing Strength, Percent drug content.[15]

RESULT AND DISCUSSION

PRELIMINARY TRIALS BASED ON EXPERIMENTAL DESIGN

Formulation F_8 was selected for the preliminary trials with the assumption that as it contained higher levels of volatilizing agent namely camphor and ammonium carbonate would produce higher response values for the variables studied. In order to enhance the process of orodispersion it was also thought to incorporate superdisintegrant Crosspovidone as well, in the formulation. Hence a preliminary trial batches PF_1-PF_4 were designed and the effect of volatilizing agent, mode of superdisintegrant addition and combination of both were studied. The results were tabulated in the table (2).

Table 2: Compiled result of disintegration time and hardness for the preliminary trial batches (PF_1-PF_4)

Trial Batch	Excipients Added	% of Excipients Added	Disintegration time (sec)	Hardness (Kg)
PF_1	Volatilizing Agent	14%(w/w)	79.8 ± 1.9	2.66 ± 0.09
PF_2	Superdisintegrant incorporated intragranularly	4%(w/w)	71.7 ± 0.8	3.5 ± 0.08
PF_3	Superdisintegrant incorporated intragranularly 2%(w/w) and Extragranularly 2%(w/w)	4%(w/w)	40.4 ± 1.4	3.1 ± 0.08
PF_4	Volatilizing Agent +Superdisintegrant	14%(w/w) 4%(w/w)	38.8 ± 0.6	2.33 ± 0.3

EFFECT OF VOLATILIZING AGENT ON DISINTEGRATION TIME AND HARDNESS OF TABLET

The trial batch PF_1 with volatilizing agent only, in the formulation showed a disintegration time of 79.87sec ±1.9sec, which was far from the limit of 60sec also the hardness of the tablet, was not sufficient (2.66kg±0.094). This indicates that incorporation of volatilizing agent alone was not sufficient to develop an acceptable orodispersible tablet with dispersion time of less than 60sec. Thus, further trials were conducted to optimize disintegration time.

EFFECT OF MODE OF INCORPORATION OF SUPERDISINTEGRANT INTRAGRANULARY AND EXTRAGRANULARLY

Trial formulation PF_2 with superdisintegrant alone incorporated intragranularly showed the disintegration time of 71.7sec±0.8 and hardness of 3.50kg±0.08. However, in the trial formulation PF_3, the superdisintegrant was incorporate both intragranularly (2%w/w) and extragranularly (2%w/w.) The disintegration time reduced to 40.4sec±1.4 with hardness of 3.10kg±0.08. This clearly indicates that to further reduce the disintegration time both volatilizing agent and superdisintegrant need to be incorporated in the formulation for desired orodispersion.

COMBINED EFFECT OF VOLATILIZING AGENT AND SUPERDISINTEGRANT

Trial batches PF_4 with both Superdisintegrant, Volatilizing agent showed a disintegration time of 38.8sec±0.6sec and hardness of 2.33kg±0.3. The trial optimized the disintegration time for the orodispersible formulation; therefore further studies were conducted using a combined approach of incorporation of both Superdisintegrant and Volatilizing Agent (intragranularly, extragranularly) in tablet formulation. However, the hardness of the tablet required improvisation.

OPTIMIZATION OF HARDNESS

Colloidal silicon dioxide was incorporated extragranularly at a level of 1%w/w in an attempt to improve the hardness of tablet. The effect of incorporation of Colloidal silicon dioxide was evidenced by an increase in the crushing strength of a tablet from a value of 2.33kg±0.3 in PF_4 to 3.1kg±0.08 PF_3. Colloidal silicon dioxide helps to restore the bonding property of excipients thereby improves the hardness of tablet.

On the basis of the result obtained from preliminary trials, the formulation F_1 to F_8 of 2^3 factorial designs was made with the following consideration

- Incorporation of both volatilizing agent and superdisintegrant.
- Superdisintegrant to be incorporated both intragranularly and extragranularly.

- Colloidal silicon dioxide was incorporated for the desired hardness without compromising the orodispersion requirement.

The compiled result of crushing strength, percent drug content and disintegration time is tabulated in the table no.

EVALUATION OF ORODISPERSIBLE TABLET

Table 3: Compiled result of disintegration time, hardness and percentage drug content for eight batches (F_1-F_8) of orodispersible tablets

Formulation	Hardness (kgs)	Disintegration time (sec)	Percent drug content
F_1	2.33 ± 0.339	1.8.38 ±0.6	97.56 ± 0.533
F_2	1.26 ± 0.41	17.32 ±1.999	58.1 ± 0.349
F_3	2.30 ± 0.374	31.88 ±6.128	98.70 ± 0.403
F_4	0.86 ± 0.094	12.14 ± 0.765	97.14 ± 0.879
F_5	4.3 ± 0.35	52.05 ± 3.507	98.42 ± 0.531
F_6	3.33 ± 0.188	27.06 ± 1.770	98.42 ± 0.531
F_7	1.66 ± 0.094	35.88 ± 7.590	97.42 ± 0.534
F_8	3.36 ± 0.205	62.01 ± 3.772	97.14 ± 0.43

SELECTION OF OPTIMIZED FORMULATION

Formulation F_5 and F_6 show the disintegration time of 52.05 sec ± 35 and 27.06 sec ± 17, which was well within the limit of less than 60sec of pharmacopoeial limit The formulation also possessed the desired hardness of 4.3 kg ± 0.35 and 3.33 kg ± 0.188 which could handling problem. The drug content of these formulations was well within the pharmacopoeial limit with 98.70% ± 0.53 and 98.42% ± 0.53. Formulation F_8 though complies with drug content test and has the desired hardness but exhibit the high disintegration time and therefore cannot be selected. Thus, the formulation F_5 and F_6 are selected on the basis of the response parameter and subjected to further evaluation.

OPTIMIZATION OF VOLATILIZATION TIME

In the present study orodispersible tablet were prepared using two different sublimizing agent e.g. camphor and ammonium bicarbonate. The two sublimizing agent are non-toxic. However, it is important to optimize the time required complete volatilization of sublimizing agent as any residual of camphor and ammonium bicarbonate in the tablet make them unpalatable. The kinetic data for residual levels of ammonium bicarbonate in formulation F5 and F6 is tabulated in table (4). When plotted on Cartesian graph a straight line was obtained suggesting a zero order volatilization. The rate of volatilization of ammonium bicarbonate was found to be 11.30 mg/hr and 9.03 mg/hr for F_5 and F_6 respectively Table (5). The straight line when extrapolated to x- axis, where concentration ammonium bicarbonate equal to zero (Fig 1 and 2) gives the time (T%) required for complete volatilization of ammonium bicarbonate. The time (T %) was determined to be 7.02hr and 7.94 hr for F5 and F6 formulation respectively. Hence subsequent formulations were subjected to volatilization period of 8hr at 50°C to ensure complete removal of ammonium bicarbonate. For the residual level studies of camphor, constant weight achieved. After 6 hrs of volatilization at 50°C indicated the complete removal of camphor from the tablet. The kinetic study justify a volatilization period of 7hr but an additional margin of 1hr was maintained to ensure complete removal of camphor and ammonium bicarbonate from tablet at 50°C. Thus 8hr was optimized as volatilization time.

Table 4: Residual levels of ammonium bicarbonate in formulation F_5 and F_6

Time (Hr)	Percent content of Ammonium Bicarbonate		Change in weight (mg)	
	F5	F6	F5	F6
0	75.981	71.318	0.25	0.25
1	69.804	64.850	0.25	0.24
2	54.893	58.879	0.24	0.23
3	42.552	47.933	0.23	0.22
4	33.296	38.978	0.21	0.20
5	22.498	28.529	0.21	0.20
6	11.701	11.598	0.21	0.20

Table 5: Rate of volatilization of ammonium bicarbonate and equation used to determine when residual level of ammonium bicarbonate becomes zero for formulation F_5 and F_6.

Formulation	Equation Used	Rate of volatilization of Ammonium Bicarbonate	Time (hr)
F_5	y = -11.30x +77.50	11.30mg/hr	7.02 hr
F_6	y = - 9.3x +74.58	9.03mg/hr	7.94 hr

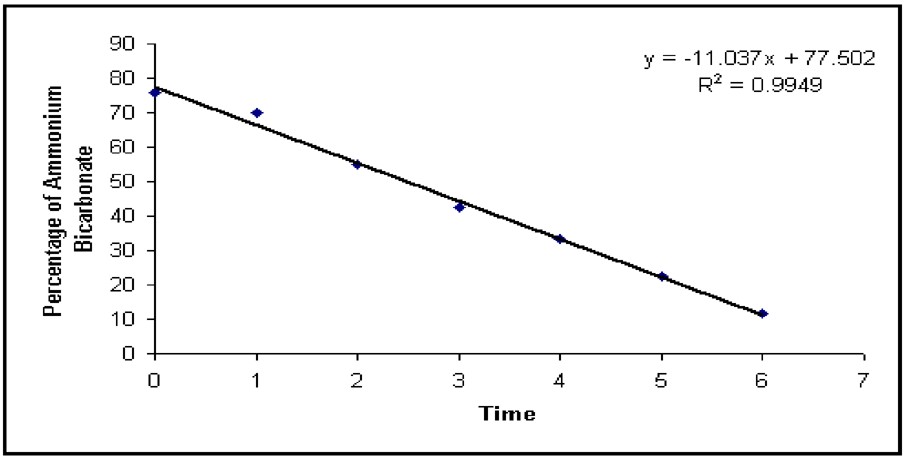


Figure1: Exponential decrease in residual level of Ammonium Bicarbonate in formulation F5

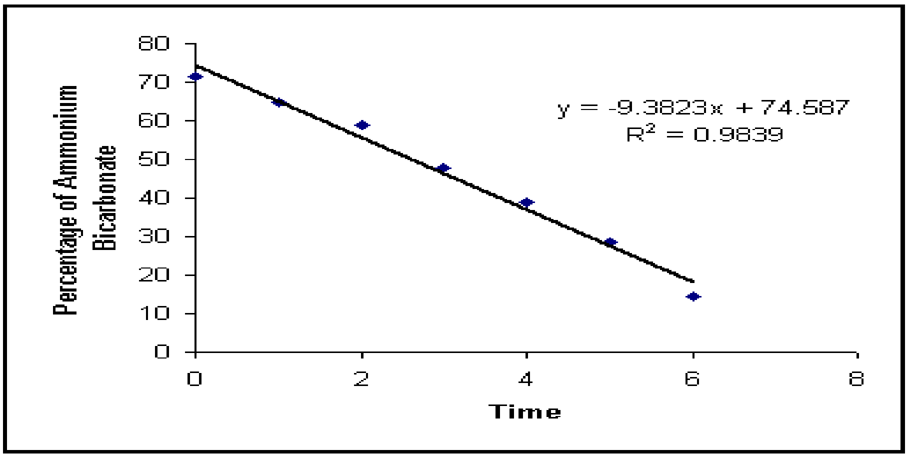


Figure1: Exponential decrease in residual level of Ammonium Bicarbonate in formulation F6

EVALUATION OF OPTIMIZED FORMULATION

SURFACE MORPHOLOGY

The scanning photograph shows the change in the surface texture of the tablet after being subjected to volatilization at 50°C for 8hrs (Fig 3). For detailed study of surface, SEM study was carried out to estimate the extent of pore formation after volatilization of camphor and ammonium bicarbonate from tablet. The SEM show the formation of pores in the matrix after sublimation of sublimizing agent, which clearly distinguished from the SEM image of tablet taken before volatilization of camphor and ammonium bicarbonate(Fig 3). The increase in the individual pore area Table (6) is also evidenced in the image. The changes observed in surface did not affect the integrity and stability of the tablet.

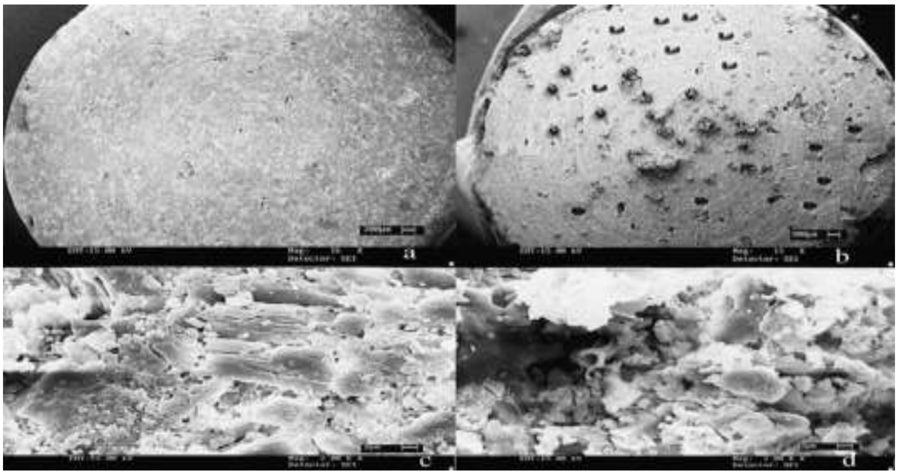


Figure. 3: SEM micrographs of prepared tablet.

(A) Before volatilization (X1600) (B) After volatilization (X1500) Tablet Surface

(C) Before volatilization (X2000) (D) After volatilization (X2000)

Table 6: Increase in pore area of tablet before and after volatilization at 50°C for 8 hrs at various magnifications.

S.No.	Magnification	Area of pore (mm^2) before volatilization	Area of pore (mm^2) after volatilization	Percentage increase in pore area
1	15X	38.01 ±1.35	101.7 ±2.51	63.315 ±8.25
2	1.00KX	0.13 ±0.92	0.66 ±1.72	
3	1.50KX	0.17 ±1.16	0.27 ±1.08	
4	2.00KX	0.11 ±2.29	0.167 ±2.73	

POROSITY, WETTING TIME AND WATER ABSORPION RATIO

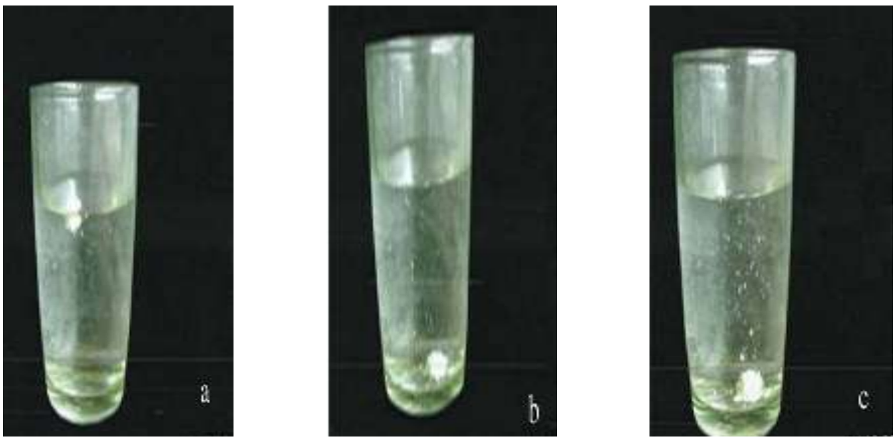
The porosity of formulated tablet was evaluated before and after volatilization of sublimizing agent at 50°C for 8hr and increase in the porosity tablet was measured. The percentage increase in porosity of two formulations after volatilization was found to be 70.51% and 77.8% Table (7). The magnitude of the increase in the porosity indicates that camphor and ammonium bicarbonate was completely volatilized and replaced by the pores in the tablet.[16] The wetting time of tablet in 10ml of water replace the disintegration time determination. This experiments increase the action of saliva in contact of tablet. The wetting time of tablet was found to be within 7 to 8sec Table (7). It was concluded that the porous structure in tablet is responsible for faster water uptake as it facilitates wicking action of Crosspovidone in bringing about fast disintegration[17]. The water absorption ratio of tablet was found to be within the range of 1 – 1.50 indicated that the formulated tablet can uptake water up to .5 times larger than its weight Table (7) This could attributed to a large number of pores and to the wicking actions of Polyplasdone XL® in the tablet.

Table 7: Wetting time, Water absorption ratio, porosity and percentage increase in porosity of formulation F_5 and F_6

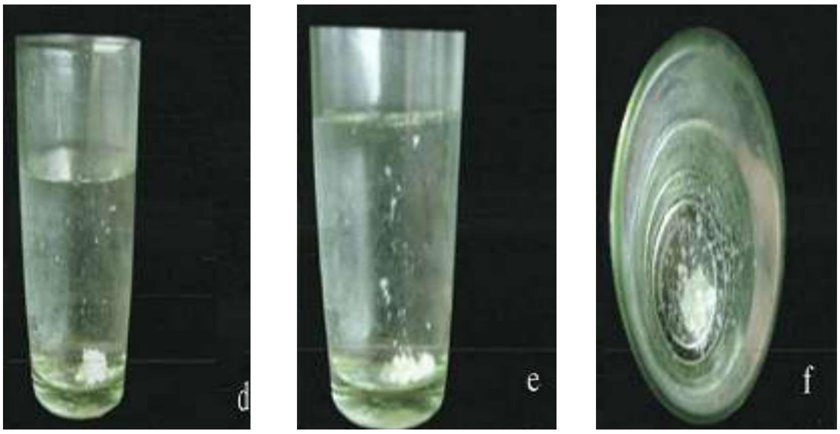
PARAMETER	(F_5)	(F_6)
Wetting time	7.80 ± 0.391	7.89 ± 0.513
Water absorption ratio	1.25 ± 0.122	1.38 ± 0.081
Porosity % **Before Volatilization** **After Volatilization**	 10.86 ± 2.022 36.82 ± 2.44	 8.35 ± 3.31 37.73 ± 3.79
% Increase in porosity after volatilization	70.517%	77.86

INVITRO DISINTREGRATION TEST

The disintegration time of formulation F_5 and F_6 was found to be 52.05 sec ±35.07 and 27.06 ± 17 which was well within the pharmacopoeial limit. Kinetic digital images of disintegration behaviour without agitation of F_6 were recorded by using digital camera and complete dispersion was obtained with 44 sec. The images are sequentially shown in fig 4.



Time: 15:25:10 **Time: 15:26:17** **Time: 15:26:29**



Time: 15:26:36 Time: 15:26:44 Time: 15:26:54

Figure 4: Digital image of Disintegration Time

INVITRO DRUG RELEASE

In vitro drug release studies were carried out for formulation F_5 and F_6, both in phosphate buffer in pH 6.4 (Salivary pH) and pH 7.4 (Physiological pH). Dissolution at salivary pH was carried out to assess the release of drug from the formulation at pH 6.4 which may add to bioavailability of Indomethacin as hepatic metabolism of drug absorbed in the buccal cavity is avoided. It was evident that in phosphate buffer pH 6.4 about 97.45% and 98.03%. Similar results were observed for the drug release behavior of orodispersion formulation in phosphate buffer pH 7.4. Here, 92.97% and 95.47% of drug was released within 60min. Faster dissolution is observed due to large surface area provided by rapid disintegration of formulation as compared to conventional tablet which require more time to disintegrate and hence to solute. Comparative dissolution profile in phosphate buffer pH 6.4 and pH 7.4 are presented in figure no. 5 and 6.

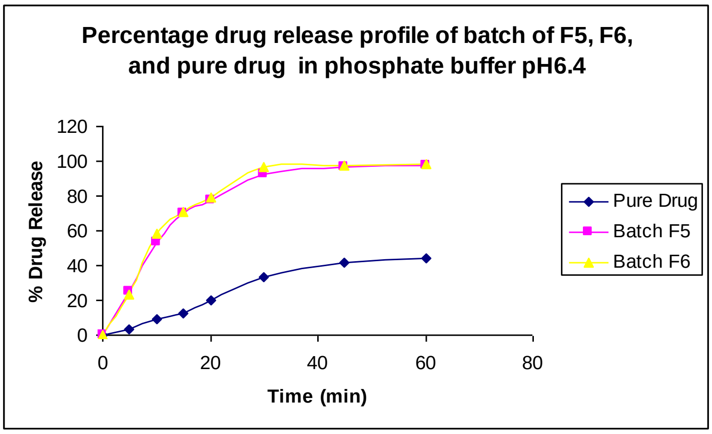


Figure 5: Drug release profile of formulation pure drug, formulation F_5 and F_6 phosphate buffer pH 6.4

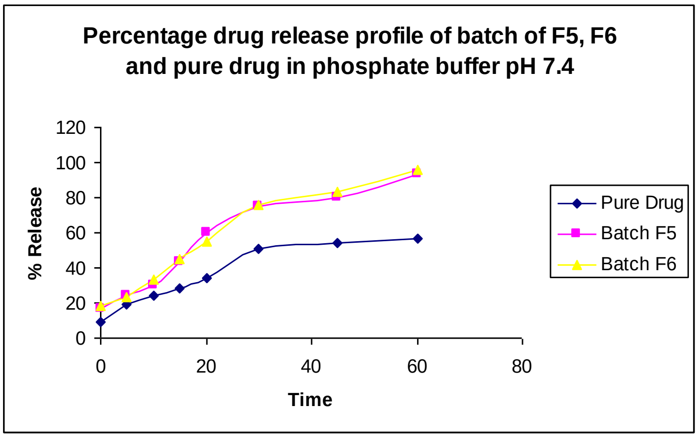


Figure 6: Invitro drug release profile of formulation pure drug, formulation F_5 and F_6 in phosphate buffer pH 7.4

Percentage dissolution efficiency was calculated to compare the dissolution profile of formulation F5, F6 and conventional tablet in phosphate buffer pH 6.4 and pH 7.4 both. The dissolution independent parameter for F5, F6 and conventional tablet are listed below in Table no. 8.

Table 8: The dissolution independent parameter for F_5, F_6 and conventional tablet

S.No	Medium	(t%)	Percentage Dissolution Efficiency		
			Pure Drug	F_5	F_6
1	Phosphate buffer pH 6.4	t20%	5.30	46.09	48.07
		t50%	17.28	74.55	76.53
		t90%	25.38	85.78	87.17
2	Phosphate buffer pH 7.4	t20%	4.94	44.90	45.71
		t50%	18.15	71.29	75.59
		t90%	24.27	81.57	84.12

STABILITY STUDIES

The stability studies of two optimized batch were carried out in accordance to ICH Q_1A guideline for three month to investigate the influence of humidity and temperature on crushing strength, disintegration time and drug content. The result shown in table(9) and (10) shows that all the tablet were chemically stable when stored in closed container at 40^{o}C ±2.0/75%RH ±5 as the drug content remained constant till end of three month. In terms of physical stability though the tablet appeared when there was a significant reduction in disintegration time and hardness for both of formulations. It may be due to the moisture absorbing capacity of mannitol Crosspovidone. These excipients most probably absorbed the moisture present in the headspace of the container. On the basis of these result it is suggested that this formulation should be stored in dry place or a suitable moisture protecting coating be done on the tablet without affecting the fundamental orodispersion process. The tablets were found to be chemically stable and the UV estimation of drug content was indicated that the absence of any degradation product in the storage condition used.

Table 9: Compiled data for stability of testing of pediatric Indomethacin formulation (F_5)

F_5	0 month	1 month	2 month	3 month
Disintegration Time (sec)	52.05±35.07	40.30±0.82	39.96±0.58	39.84±0.18
Hardness (Kg)	4.3±0.3	3.93±0.04	3.76±0.11	3.43±0.05
Drug Content (%)	98.42±0.531	97.54±0.65	98.68±0.49	97.41±0.50

Table 10: Compiled data for stability of testing of pediatric Indomethacin formulation (F6)

F_6	0 month	1 month	2 month	3 month
Disintegration Time (sec)	27.06 ±176	26.77 ±0.82	26.47 ±0.58	26.33 ±0.8
Hardness (Kg)	3.33 ±0.18	3.33 ±0.04	3.33± 0.11	3.30 ±0.33
Drug Content (%)	98.42 ±0.531	97.54 ±0.65	98.24±0.49	97.11 ±0.12

CONCLUSION

In the present study, Indomethacin is a nonsteroidal anti-inflammatory drug was chosen as model drug for formulation into pediatric orodispersible tablet. Design of experiment were based on 2^3 factorial design and total of eight batches of tablet was formulated. Highly porous tablet with acceptable mechanical strength were formulated by direct compression technique using a combination of sublimizing agent and superdisintegrant in the formulation. Camphor and ammonium bicarbonate were chosen as sublimizing agents which were subjecting volatilization at 50^{0}C for 8hrs from the tablet matrix. Orodispersible tablet were evaluated for disintegration time using modified disintegration apparatus showed disintegration time less than 60sec which is in accordance to European Pharmacopoeia. Preliminary trial were carried out to study the effect of volatilizing agent on disintegration time and hardness of tablet, to study the effect of mode of incorporation of superdisintegrant, intragranular and/ or extragranular to study combined effect of volatilizing agent and superdisintegrant to optimize hardness. 1% colloidal silicon dioxide was added to improve the hardness of the tablet without affecting the dispersion time. Wetting time, Water absorption ratio, Porosity drug content, and In vitro drug release in phosphate buffer (pH 6.4 and pH 7.4) were investigated. The percentage release was found to be 97.45 and 98.03 for formulation F_5 and 92.97 and 95.47 for formulation F_6 within 30min in phosphate buffer pH 6.4 and phosphate buffer pH 7.4 respectively which was many fold higher than the release of Indomethacin from the conventional tablet. Surface morphology of prepared orodispersible tablet was investigated by scanning photograph and its SEM. Kinetic digital images were recorded to study the disintegration process of prepared tablet. The disintegration time was found to be 44 sec. Factorial design was validated by extra design checkpoints studies. Formulation F5 and F6 were identified as optimized formulation. The stability studies were carried out in accordance to ICH Q_1A guideline for six month to investigate the influence of humidity and temperature on the crushing strength, disintegration time and drug content.

The tablets were found to be chemically stable but there was a significant reduction in disintegration time and hardness for both the formulation. It may be due to the moisture absorbing capacity of mannitol and Crosspovidone. These excipients probably absorbed the moisture present in the headspace of the closed container. On the basis of these result it is suggested that this formulation should be stored in dry place or a suitable moisture protecting coating be done on the tablet within out affecting the fundamental orodispersion process. To enhance the elegance of the tablet for the pediatric patients, it is recommended for film coating with suitable coating material without effecting the disintegration time and other parameter of the orodispersion tablet.

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