



# Formulation and Evaluation Oral Dispersible Tablets of Vidarabine

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## Abstract

In the present work, taste masking of Vidarabine was carried out by using HP- $\beta$ -CD inclusion complex. These taste-masked complexes were further formulated into the Oro dispersible tablet by the direct compression method using Ac-Di-Sol and Avicel as a super disintegrant. Vidarabine is used in the treatment of AIDS. This research has described the production of a taste masked dosage form from initial determination of threshold bitterness concentration of the pure drug through to the development of a final taste masked prototype formulation. It was found that the taste masked 1:2 ratio of LMV: HP- $\beta$ -CD inclusion complex increases the bulk of final ODT blend (above 1000 mg) which is not feasible for formulation of ODTs. So, in this study the ODTs of LMV: HP- $\beta$ -CD inclusion complex (1:1 ratio) showing acceptable bitterness in human taste panel studies was used in formulation of ODTs. In all formulations, the dispersion produced was soft (without grittiness) with a good mouth feel, and the bitter taste was fully masked. *In vitro* drug release profile of all optimized ODT formulations showed around 90% of drugs release within 10 to 15 minutes in acidic buffer (pH 1.2), implying that the drug will be absorbed fast, increasing the chances of bioavailability. A three-month stability analysis was carried out. For the optimized formulations, there was no noticeable difference in disintegration time, hardness, friability, or drug content.

## Keywords

Vidarabine, super disintegrant, Orodispersible.

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## INTRODUCTION:

Oral is the most preferred route of drug administration but is not suitable for patients with dysphagia. To overcome this problem or dispersible tablets is one of the famous technological innovations in the contract manufacturing and pharmaceutical field. Taste masking and taste assessment are the two main factors taken into consideration while formulating ODTs as they disintegrate and/ or dissolve in oral cavity. Taste masking in addition is related to patient compliance. Patient compliance is particularly important in pediatrics, geriatric, and long drug therapy patients.

An ODT is a drug dosage form available for a small variety of over the counter (OTC) and prescription drugs (4). ODT disintegrates and/ or dissolves rapidly in the mouth without the need for water, which makes it suitable during traveling without immediate access to water. Since swallowing the saliva containing the dissolved or dispersed medication, the drug is consumed normally. Any drugs in ODT are showing fast onset of action and improved bioavailability as compared to same drugs in traditional tablet dosage form. This is due to ODTs pre-gastric absorption. ODT is also the best formulation option for drugs with a first-pass effect.

## METHODS

### Formulation of ODTs of Vidarabine-HP-β-CD Complex.

After adding superdisintegrants such as croscarmellose sodium (Ac-DI-Sol), sodium starch glycolate (SSG), and a mixture of both in different concentrations, orodispersible tablets of drug: polymer complex was prepared using the direct compression process. As the optimized ratio 1:2 of

LMV: HP β-CD complex in the optimization increased the total bulk of ODT, was not selected for further formulation of ODTs of LMV-HP β-CD Complexes. So, the three formulations of LMV: HP β-CD (1:1) complex (which is batch F1 in Table 4-10) were prepared. Mannitol (Perreck M) and microcrystalline cellulose (Avicel PH 102) were mixed thoroughly in a glass mortar using a pestle.

**Table 1: Formulation of ODTs of LMV: HP β-CD Complex**

Ingredients (Quantity in mg)	F4	F5	F6
LMV-HP β-CD (1:1) equivalent to 100 mg Vidarabine.	676.73	676.73	676.73
Microcrystalline Cellulose PH 102	120	120	120
Sodium Starch Glycolate (SSG)	10	--	--
Croscarmellose Sodium (CCS)	--	10	--
SSG+ CCS	--	--	10
Mannitol	05	05	05
Magnesium Stearate	04	04	04
Talc	04.27	04.27	04.27
Tablet Weight	820	820	820

## Results and Discussion

### Vidarabine (Azidothymidine)- HP-β-CD Inclusion Complex Formation by Kneading Method

#### Experimental Design:

The effect of factors X1 and X2 is found to be statistically significant in nature. Response variables i.e., entrapment efficiency and drug content are simultaneously optimized using desirability function using Design Expert software. This process allows the selection of the most suitable level of factors to

achieve desired level of drug content and entrapment efficiency. The results of multiple linear regression analysis revealed that for obtaining desirable drug content (91.76%) and entrapment efficiency (more than 67.07%), the formulation should be prepared using 1:2 drug polymer ratio with kneading time of 40 minutes.

**Table 2: Independent factors in LMV- HP-Beta CD complexation.**

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	LMV: HP Beta CD ratio	2.1754	1	3	0	Actual
B	Kneading time	43.1885	30	50	0	Actual

**Table 3: Design Summary of LMV- HP-Beta CD complexation.**

Standard	Run	LMV: HP Beta CD ratio	Kneading time	Entrapment efficiency	Drug content
4	1	1	40	76.44	75.9
10	2	2	40	98.66	90.57
2	3	2	30	86.14	67.48
11	4	2	40	97.81	91.11
6	5	3	40	87.85	81.22
5	6	2	40	98.36	91.02
13	7	2	40	96.98	91.21
7	8	1	50	81.02	73.26
8	9	2	50	96.32	79.61
12	10	2	40	98.11	91.76
9	11	3	50	89.96	83.86
1	12	1	30	74.03	67.07
3	13	3	30	88.49	74.38

### Effect on Entrapment Efficiency

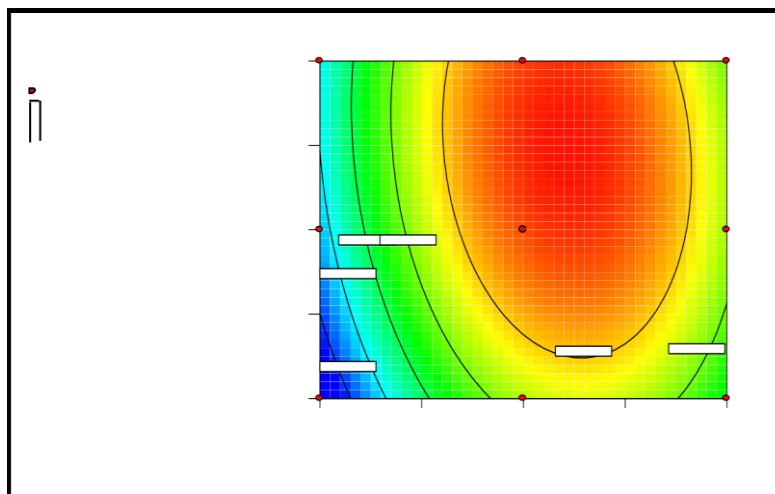


Figure 1: Interaction effect plot

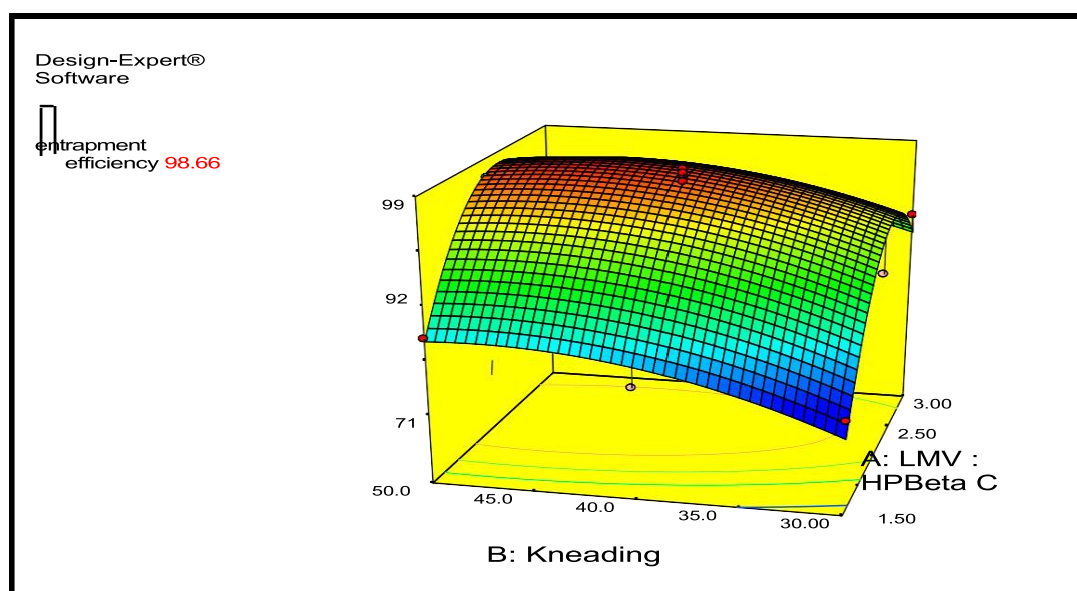


Figure 2: Response surface plot

### Sensory Test on Threshold Value of Bitter Taste for Vidarabine/ LMV

Sensory test was performed to determine threshold bitterness concentration of Vidarabine on concentrations 5, 10, 20, 30, 40, 60 and 80  $\mu\text{g/ml}$ .

Table 1: Sensory Test for Determination of Threshold Bitterness Concentration for LMV

No. of volunteer	Concentration ( $\mu\text{g/ml}$ )						
	5	10	20	30	40	60	80
1	0	0	0	0	1	1	3
2	0	0	0	0	0	1	3
3	0	0	0	0	1	2	2
4	0	0	0	0	0	2	3
5	0	0	0	0	0	2	3
6	0	0	0	0	2	1	3

### ***In vitro* taste masking evaluation of LMV-HP- $\beta$ -CD (1:1) complex**

**Table 2: *In vitro* taste masking evaluation of LMV-HP- $\beta$ -CD (1:1) complex in phosphate buffer pH 6.8.**

Time (sec.)	Concentration ( $\mu$ g/ml)			
	1	2	3	Average
30	10.56	12.05	11.34	11.31
60	17.74	17.27	19.38	18.13
120	29.84	30.41	29.30	29.85

Threshold Bitterness Concentration for Vidarabine was found to be 40 g/ml. *In vitro* release of Vidarabine from LMV-HP- $\beta$ -CD (1:1) complex was 29.85 g/ml below threshold bitterness concentration i.e., 40 g/ml up to period of 120 seconds.

### ***In vitro* taste masking evaluation of LMV: indion 234 (1:1.5) complex**

**Table 3: *In vitro* taste masking evaluation of LMV: indion 234 (1:1.5) complex in phosphate buffer pH6.8.**

Time (sec.)	Concentration ( $\mu$ g/ml)			
	1	2	3	Average
30	9.82	10.21	10.41	10.15
60	15.91	15.72	16.21	15.95
120	22.94	22.80	22.99	22.91

Threshold Bitterness Concentration for Vidarabine was found to be 40 g/ml. *In vitro* release of Vidarabine from LMV: indion 234 (1:1.5) complex was 22.91 g/ml below threshold bitterness concentration i.e., 40 g/ml upto time period of 120 seconds.

### ***In vivo* Taste Evaluation of LMV-HP- $\beta$ -CD complexes.**

The taste of the drug and complex was checked by time intensity method. The six healthy human volunteers were used for taste masking and

informed consent was obtained from all of them. Bitterness was measured by consensus of a trained taste panel, with 20mg of sample held in the mouth for 5 to 10 sec., then spat out: the bitterness level was then recorded.

These volunteers were instructed not to swallow the granules, which were placed on the tongue. They were instructed to thoroughly gargle their mouth with distilled water after the completion of the test.

**Table 4: *In-vivo* Taste Evaluation of LMV-HP- $\beta$ -CD complexes.**

Batch	Drug (LMV)						LMV-HP- $\beta$ -CD complex					
	V1	V2	V3	V4	V5	V6	V1	V2	V3	V4	V5	V6
F1	4	3	4	4	4	4	0	0	1	0	1	1
F2	4	3	4	4	4	4	1	1	0	0	1	1
F3	4	3	4	4	4	4	2	1	1	1	1	1
F4	4	3	4	4	4	4	1	1	2	1	1	1
F5	4	3	4	4	4	4	0	0	0	0	0	0
F6	4	3	4	4	4	4	0	0	0	0	0	0
F7	4	3	4	4	4	4	0	1	0	0	0	1
F8	4	3	4	4	4	4	0	0	0	0	0	0
F9	4	3	4	4	4	4	0	0	0	0	0	0

**Table 5: *In-vivo* Taste Evaluation of LMV: Indion 234 (1:1.5) complex.**

Volunteers	Bitterness level after taste masking					
	10 sec	1 min	2 min	4 min	6 min	8 min
1	0	0	0	0	0	0
2	0	0	0	0	1	1
3	0	0	0	0	0	2
4	0	0	0	0	1	2
5	0	0	0	0	0	0
6	0	0	0	0	0	0

7	0	0	0	0	1	1
8	0	0	0	0	0	0
9	0	0	0	0	0	0
10	0	0	0	0	0	0

**Table 6: Volunteers Opinion Test for Vidarabine before and after Taste Masking (n=10)**

Time (seconds)	Before taste masking	After taste masking
	Mean $\pm$ SD	Mean $\pm$ SD
10	1.9*** $\pm$ 0.38	0
60	2.5*** $\pm$ 0.42	0
120	3.0*** $\pm$ 0.42	0
240	3.4*** $\pm$ 0.51	0
360	3.8*** $\pm$ 0.43	0.3*** $\pm$ 0.84
480	4.0*** $\pm$ 0.48	0.6*** $\pm$ 0.63

#### Determination of Drug Content in the Drug-Polymer Complex

##### Drug content of LMV: indion 234 (1:1.5) complex.

The resinate prepared (containing 10 mg of LMV) was subjected to evaluation of drug content and the data

obtained is shown in Table 7. It was observed that the practical concentration obtained was  $9.91 \pm 0.043$  mg, which was almost 99.1 % of theoretical concentration that is 10 mg.

**Table 7: Drug content of LMV: indion 234 (1:1.5) complex**

Name of Complex	Theoretical Conc. (mg)	Practical Conc. (mg)	% Drug Content
Vidarabine: Indion 234	10	$9.91 \pm 0.043$	99.1 %

#### Evaluation of Oro dispersible Tablets

##### Pre-Compression Studies

The directly compressible tablet blends were evaluated for pre-compression studies to determine their flow and compressibility (86).

**Table 8: Micromeritic Properties of tablet blends containing optimized drug: polymer complexes (n= 3)**

Property	LMV: HP- $\beta$ -CD	LMV: Indion 234
Carr's Index (%)	$13.6 \pm 0.15$	$16.90 \pm 0.72$
Bulk Density (g/ml)	$0.532 \pm 0.93$	$0.473 \pm 1.19$
Angle of Repose (0)	$25.420 \pm 0.77$	$16.7 \pm 0.691$

#### Post-Compression Studies

**Table 9: Evaluation of ODTs of LMV: HP- $\beta$ -CD Complex**

Test	F1	F2	F3
Weight variation test	$170.0 \pm 1.4$	$170.4 \pm 1.2$	$170.2 \pm 1.6$
Hardness (Kg/cm <sup>2</sup> )	$3.5 \pm 0.09$	$3.75 \pm 0.08$	$4.00 \pm 0.10$
Friability (%)	0.84	0.80	0.72
Drug content (%)	$100.8 \pm 0.20$	$100.6 \pm 0.56$	$99.90 \pm 0.10$
Wetting time (Seconds)	$45 \pm 1.00$	$37 \pm 1.53$	$30 \pm 2.00$
Mouth feel	-	-	-
<i>In vivo</i> disintegration time (Seconds)	$57 \pm 1.97$	$48 \pm 1.86$	$30 \pm 1.37$
<i>In vitro</i> dispersion time (Seconds)	$42 \pm 1.00$	$38 \pm 2.00$	$25 \pm 1.53$

#### *In vitro* release profile of formulated tablets:

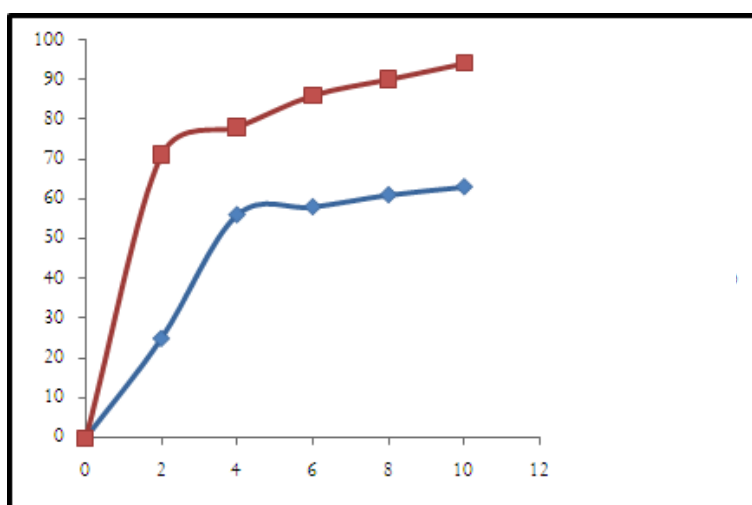
The dissolution test of tablets was performed using acidic buffer pH 1.2 with USP dissolution type II apparatus at 100 rpm and  $37 \pm 0.50^\circ\text{C}$  temperatures.

Test sample (5 ml) was withdrawn at a particular time interval and replaced with fresh dissolution media maintained at  $37 \pm 0.50^\circ\text{C}$ . The test sample was filtered through membrane filter having size  $0.45 \mu\text{m}$

and analyzed using UV spectrophotometer at  $\lambda_{max}$  values. This test was performed on successive three tablets and mean  $\pm$  SD calculated.

**Table 10: *In vitro* Dissolution Study of Retrovir Vs optimized ODTs Batch F6**

Sr. No.	Time (min.)	Retrovir	LMV-HP- $\beta$ -CD ODTs
1	2	24.23 $\pm$ 0.21	71.46 $\pm$ 0.68
2	4	55.62 $\pm$ 0.73	78.26 $\pm$ 0.34
3	6	58.43 $\pm$ 0.22	86.21 $\pm$ 0.96
4	8	60.62 $\pm$ 0.18	89.80 $\pm$ 0.32
5	10	62.68 $\pm$ 0.27	93.66 $\pm$ 0.66

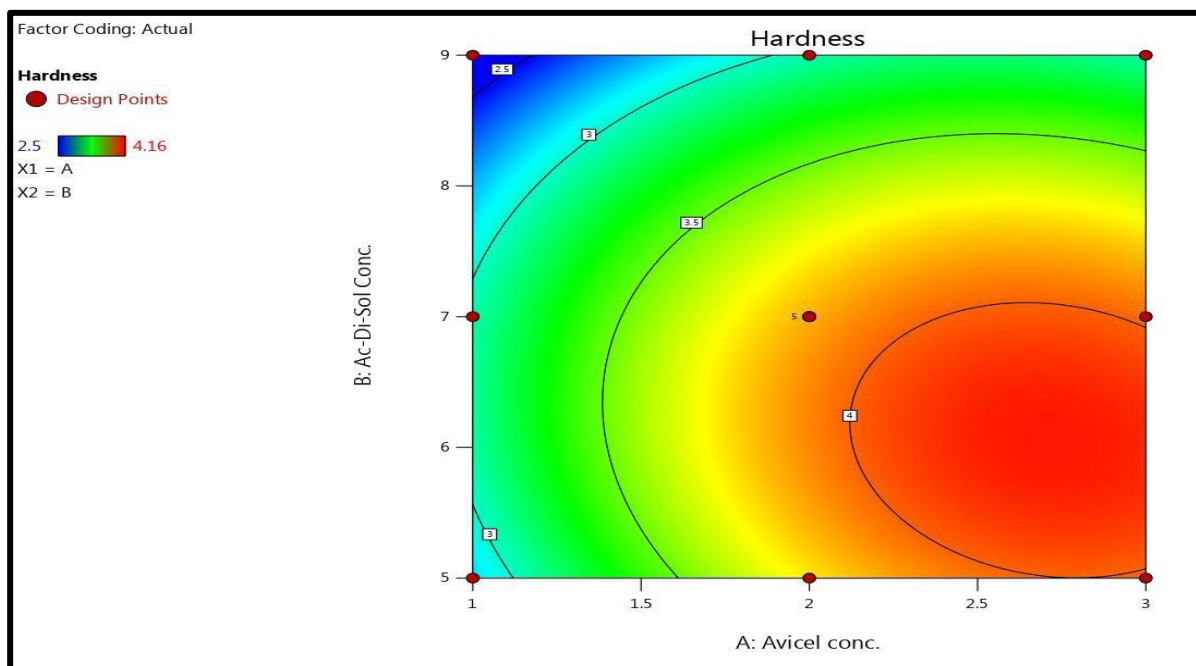


**Figure 1: *In-vitro* Dissolution Study of Retrovir Vs optimized ODTs Batch F6**

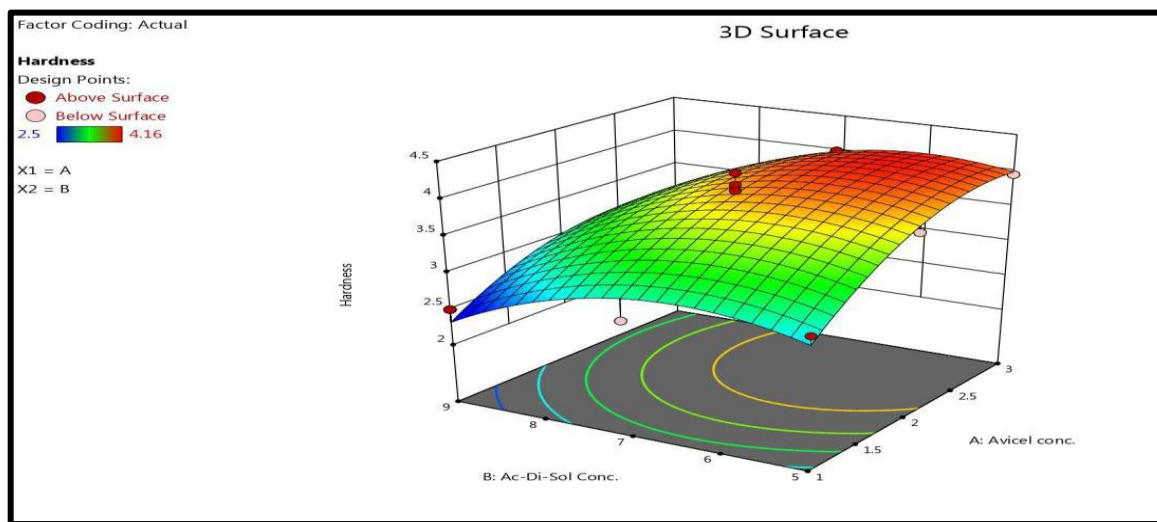
**Table 11. Design summary of ODTs containing Vidarabine: indion234 (1:1.5) complex.**

Batch No.	Avicel conc.	Ac-Di- Sol conc.	Hardness	Friability	Disintegration time
1	1	7	2.75	0.59	28
2	1	5	2.97	0.33	32
3	2	7	4	0.59	24
4	3	9	3.08	0.59	16
5	2	9	2.84	0.64	14
6	2	7	3.92	0.54	21
7	3	7	3.99	0.4	31
8	2	7	4.16	0.48	20
9	2	5	3.69	0.22	42
10	2	7	3.82	0.57	20
11	1	9	2.5	0.71	15
12	2	7	3.75	0.57	19
13	3	5	3.95	0.39	57

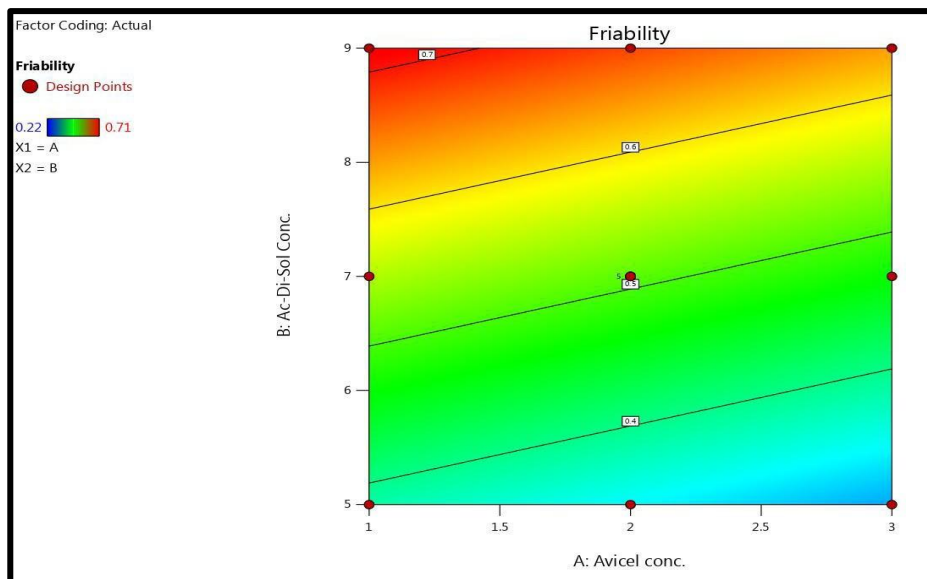
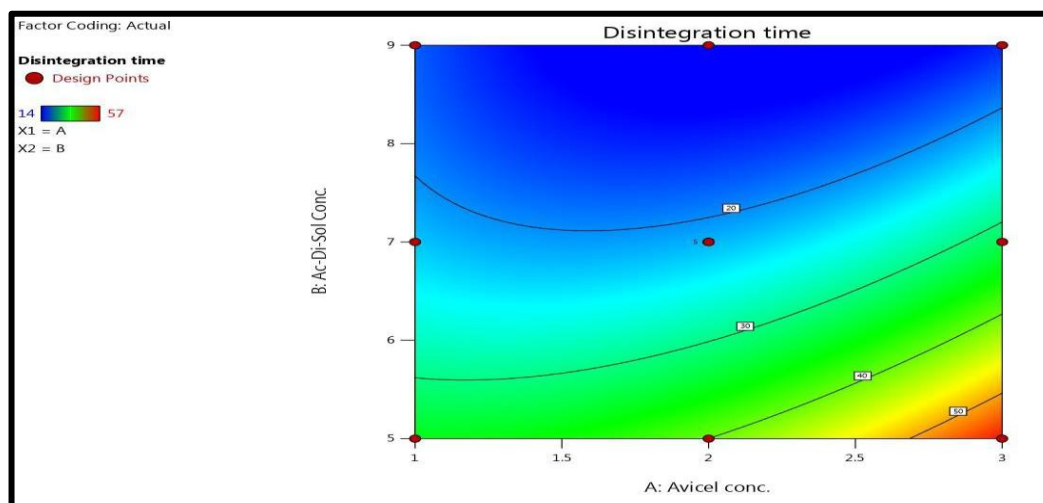
**Effect on Hardness (Y1)**



**Figure 2: Interaction effect plot for hardness**

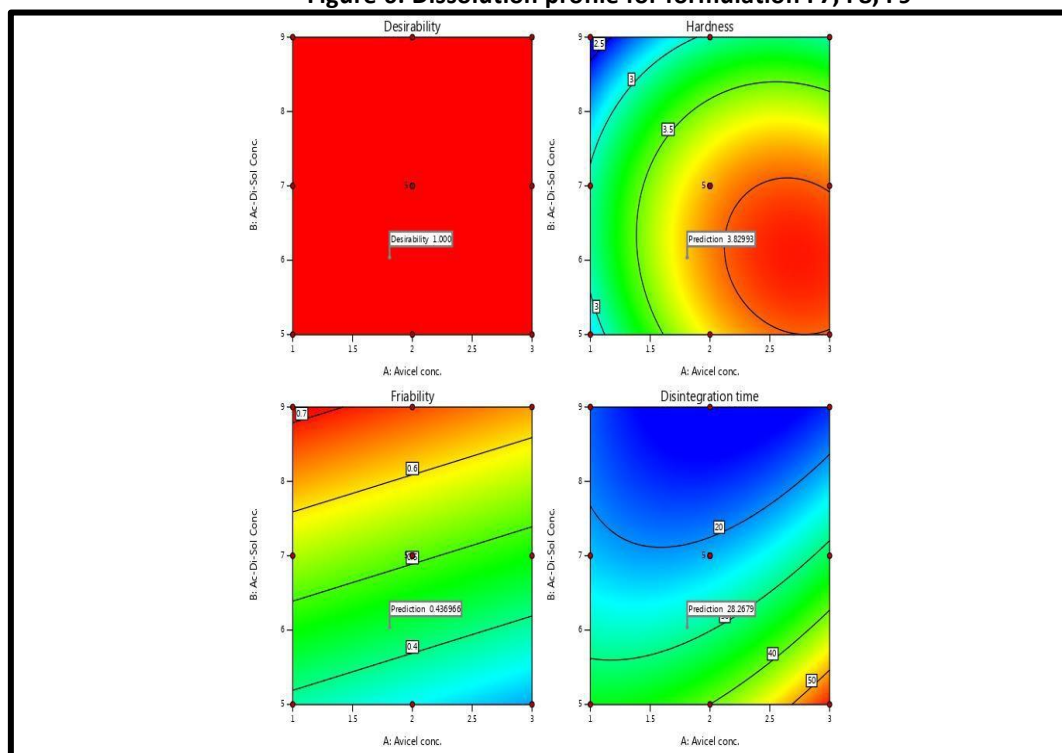


**Figure 3: Response surface plot for hardness**

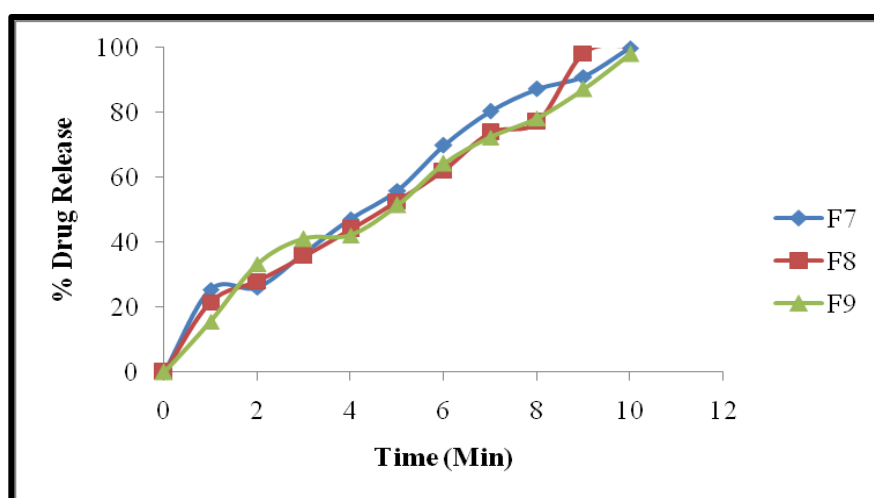
**Effect on Friability (Y2)**
**Figure 4: Interaction effect plot for friability**

**Effect on disintegration time (Y3)**
**Figure 5: Interaction effect plot for disintegration time**

**Table 12: Response coefficient table for ODTs of LMV: Indion 234 complex.**

	Intercept	A	B	AB	A <sup>2</sup>	B <sup>2</sup>
<b>Hardness</b>	3.87207	<b>0.466667</b>	<b>-0.365</b>	-0.1	<b>-0.357241</b>	<b>-0.462241</b>
<b>p-values</b>		<b>0.0009</b>	<b>0.0037</b>	0.3702	<b>0.0250</b>	<b>0.0079</b>
<b>Friability</b>	0.509231	-0.0416667	<b>0.166667</b>			
<b>p-values</b>		0.1835	<b>0.0002</b>			
<b>Disintegration time</b>	21.7241	<b>4.83333</b>	<b>-14.3333</b>	-6	<b>5.46552</b>	3.96552
<b>p-values</b>		<b>0.0098</b>	<b>&lt; 0.0001</b>	<b>0.0092</b>	<b>0.0308</b>	0.0913



**Figure 6: Dissolution profile for formulation F7, F8, F9**

**Table 13: Evaluation of Orodispersible Tablets of Vidarabine: Indion 234 Resin Complex**

Test	F7	F8	F9
Weight variation test	400.0±0.89	409.4±1.11	403.2±0.94
Hardness (Kg/cm <sup>2</sup> )	3.5±0.09	3.75±0.08	4.00±0.10
Friability (%)	0.57	0.47	0.49
Drug content (%)	95.69±0.20	98.60±0.56	99.90±0.10
Wetting time (Seconds)	63±1.54	44±1.10	42±2.00
Mouth feel	-	-	-
<i>In vivo</i> disintegration time (Seconds)	47±1.84	41±1.06	50±1.37
<i>In vitro</i> dispersion time (Seconds)	32±1.00	29±2.00	39±1.53



**Table 14: Dissolution data for formulation F7 to F9**

Time (Min)	F7	F8	F9
0	0	0	0
1	25.50±1.30	21.50±1.32	15.58±0.98
2	26.16±0.70	28.02±1.06	33.36±2.45
3	36.75±0.58	35.77±0.86	41.11±3.51
4	47.02±1.57	43.89±0.66	42.23±3.80
5	55.89±2.21	52.70±0.14	51.58±3.30
6	69.89±3.44	62.16±1.35	64.26±2.76
7	80.43±3.50	73.87±0.68	72.33±3.98
8	87.29±2.49	77.15±2.32	78.29±2.39
9	91.09±1.76	98.34±0.23	87.29±2.49
10	99.88±0.33	100.81±0.32	98.09±1.76

**Accelerated Stability Studies of the Optimized ODTs.**

Accelerated stability studies were carried out according to an International Conference on Harmonization (ICH) guidelines. The optimized formulations were placed in aluminum capped transparent glass vials for three months under storage conditions of 450C±20C and 75%±5%. At the

end of each month, these samples were removed and analyzed for post compression tests.

The stability analysis showed that all the formulations were physically stable when maintained at 450C±20C and 75%±5% RH for three months, with no major differences in the findings. (88).

**Table 15: Table 5-49: Effect of Stability Studies on ODTs Prepared by Using LMV-HP-β-CD Inclusion Complex (1:2)**

Parameters Evaluated	1stmonth		2ndmonth		3rdmonth	
	Storage Condition		Storage Condition		Storage Condition	
	30±2°C / 60±5%RH	40±2°C / 75±5%RH	30±2°C / 60±5%RH	40±2°C / 75±5%RH	30±22 °C/ 60±5%RH	40±2°C/ 75±5%RH
<b>Hardness (kg/cm<sup>2</sup>)</b>	4.2 ±0.07	4.7 ±0.18	4.0 ±0.19	4.5 ±0.21	4.5 ±0.13	5.5 ±0.19
<b>Friability (%)</b>	0.89	0.69	0.75	0.78	0.88	0.51
<b>In Vitro Dispersion Time (sec)</b>	39 ±0.25	42 ±0.09	40 ±0.18	45 ±0.11	39 ±0.18	44 ±0.19
<b>Drug Content (%)</b>	99.70 ±0.10	100.42 ±0.17	99.89 ±0.35	98.12 ±0.67	99.87 ±0.25	99.39 ±0.38

**Table 16: Effect of Stability Studies on ODTs Prepared by Using LMV-Indion 234 Complex (1:1.5)**

Parameters Evaluated	1 <sup>st</sup> month		2 <sup>nd</sup> month		3 <sup>rd</sup> month	
	Storage Condition		Storage Condition		Storage Condition	
	30±2°C / 60±5%RH	40±2°C / 75±5%RH	30±2°C / 60±5%RH	40±2°C / 75±5%RH	30±22 °C/ 60±5%RH	40±2°C/ 75±5%RH
<b>Hardness (kg/cm<sup>2</sup>)</b>	3.9 ±0.07	4.6 ±0.18	3.57 ±0.19	4.2 ±0.21	4.1 ±0.13	5.2 ±0.19
<b>Friability (%)</b>	0.49	0.37	0.51	0.42	0.73	0.44
<b>In Vitro Dispersion Time (sec)</b>	39 ±0.18	41 ±0.21	36 ±0.11	39 ±0.16	41 ±0.18	47 ±0.07

Drug Content (%)	95.70 ±0.15	98.42 ±0.09	98.98 ±0.21	99.12 ±0.94	96.87 ±0.17	99.53 ±0.07
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### SUMMARY AND CONCLUSION

Oral is the most preferred route of drug administration but is not suitable for patients with dysphagia. To overcome this problem orodispersible tablets is one of the famous technological innovations in the contract manufacturing and pharmaceutical field. Taste masking and taste assessment are the two main factors taken into consideration while formulating ODTs as they disintegrate and/ or dissolve in oral cavity. Taste masking in addition is related to patient compliance. Patient compliance is particularly important in pediatrics, geriatric and long drug therapy patients. It was found that the taste masked 1:2 ratio of LMV: HP- $\beta$ -CD inclusion complex increases the bulk of final ODT blend (above 1000 mg) which is not feasible for formulation of ODTs. So, in this study the ODTs of LMV: HP- $\beta$ -CD inclusion complex (1:1 ratio) showing acceptable bitterness in human taste panel studies was used in formulation of ODTs.

*In vitro* drug release profile of all optimized ODT formulations showed around 90% of drugs release within 10 to 15 minutes in acidic buffer (pH 1.2), implying that the drug will be absorbed fast, increasing the chances of bioavailability. A three-month stability analysis was carried out. For the optimized formulations, there was no noticeable difference in disintegration time, hardness, friability, or drug content.

Overall, this study concludes that taste masked ODTs of the drug Vidarabine not only improve patient compliance but also overcome neglected dysphagia associated with these two drug therapies. A greater understanding of patient compliance in any of the drug treatments will allow proper formulations to be developed which in turn will improve treatment outcomes.

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