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FORMULATION AND EVALAUATION ORAL DISPERSIBLE TABLETS OF VIDARABINE

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Abstract:

*In the present work, taste masking of **Vidarabine** was carried out by using HP-β-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 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-β-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-β-CD inclusion complex (1:1 ratio) showing acceptable bitterness in human taste panel studies was used in formulation ofODTs. 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 ofbioavailability. 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 the 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 dissolves in oral cavity. Taste masking in addition is related to patient compliance. Patient compliance is particularly important in pediatrics, geriatric and long drug therapypatients.

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 pregastric absorption. ODT is also the best formulation option for drugs with a first-passeffect.

METHODS

Formulation of ODTs of Vidarabine-HP-β-CDComplex.

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 were 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 (Perteck 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 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 :HPBeta 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 :HPBeta 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

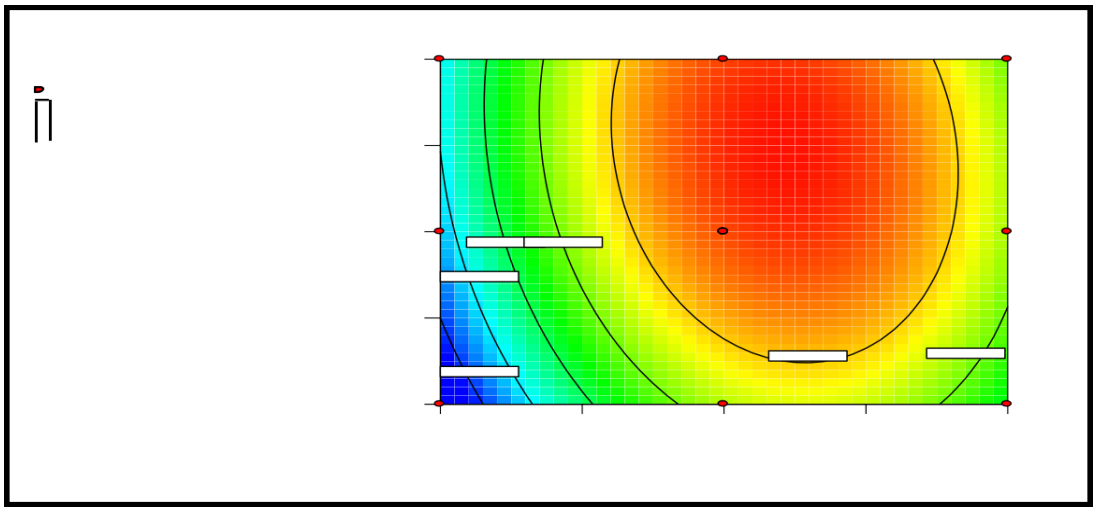


Figure 1: Interaction effect plot

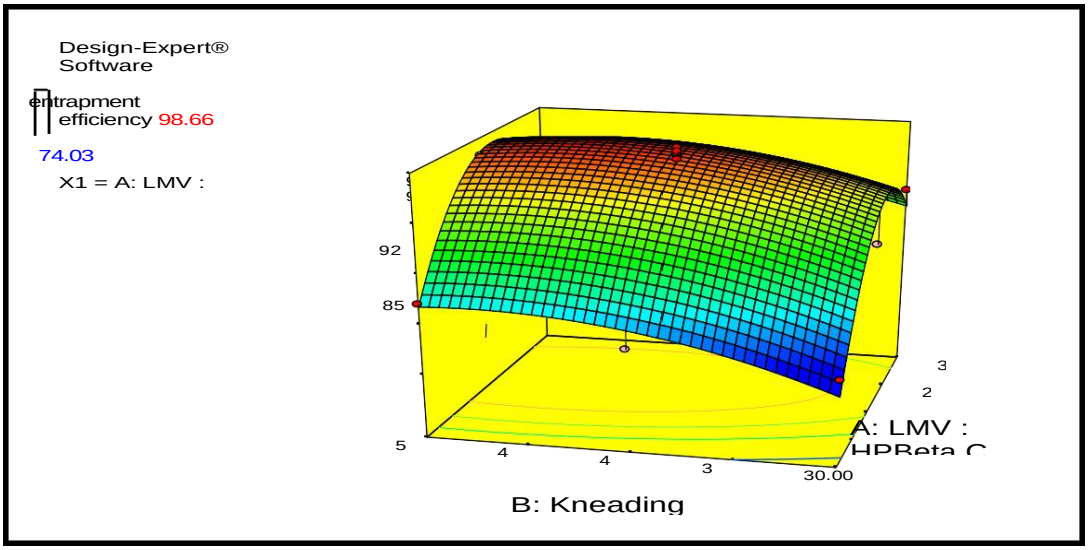


Figure 2: Response surface plot

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 and80µg/ml.

Table 4: Sensory Test for Determination of Threshold Bitterness Concentration for LMV

No. of volunteer	Concentration (□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-β-CD (1:1) complex**

Table 5: In vitro taste masking evaluation of LMV-HP-β-CD (1:1) complex in phosphate buffer pH 6.8.

Time (sec.)	Concentration (□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-β-CD (1:1) complex was 29.85 g/ml below threshold bitterness concentration i.e. 40 □g/ml upto time period of 120 seconds.

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

Table 5: In vitro taste masking evaluation of LMV: indion 234 (1:1.5) complex in phosphate buffer pH6.8.

Time (sec.)	Concentration (□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-β-CDcomplexes.

Taste of 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 test.

Table 6: In-vivo Taste Evaluation of LMV-HP-β-CD complexes.

Batch	Drug (LMV)						LMV-HP-β-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 7: *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 8: Volunteers Opinion Test for Vidarabine before and after Taste Masking (n=10)

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

Determination of Drug Content in the Drug-PolymerComplex

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

The resinate prepared (containing 10 mg of LMV) was subjected for evaluation of drug content and the data obtained is shown in Table 7. It was observed that the practical concentration obtained was 9.91 ± 0.043 mg, which was almost 99.1 % of theoretical concentration that is 10 mg.

Table 9: 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 ± 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 10: Micromeritic Properties of tablet blends containing optimized drug: polymer complexes (n= 3)

Property	LMV: HP-β-CD	LMV: Indion 234
Carr's Index (%)	13.6± 0.15	16.90 ± 0.72
Bulk Density (g/ml)	0.532± 0.93	0.473± 1.19
Angle of Repose (^{0})	25.42^0± 0.77	16.7 ± 0.691

Post-Compression Studies

Table 11: Evaluation of ODTs of LMV: HP-β-CDComplex

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

In vitro release profile of formulated tablets:

Dissolution test of tablets was performed using acidic buffer pH 1.2 with USP dissolution type II apparatus at 100 rpm and 37 ± 0.5^{0}C temperatures. Test sample (5 ml) was withdrawn at a particular time interval and replaced with fresh dissolution media maintained at 37 ± 0.5^{0}C. The test sample was filtered through membrane filter having size 0.45 µm and analyzed using UV spectrophotometer at λ_{max} values. This test was performed on successive three tablets and mean ± SDcalculated.

Table 12: In- vitro Dissolution Study of Retrovir Vs optimized ODTs Batch F6

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

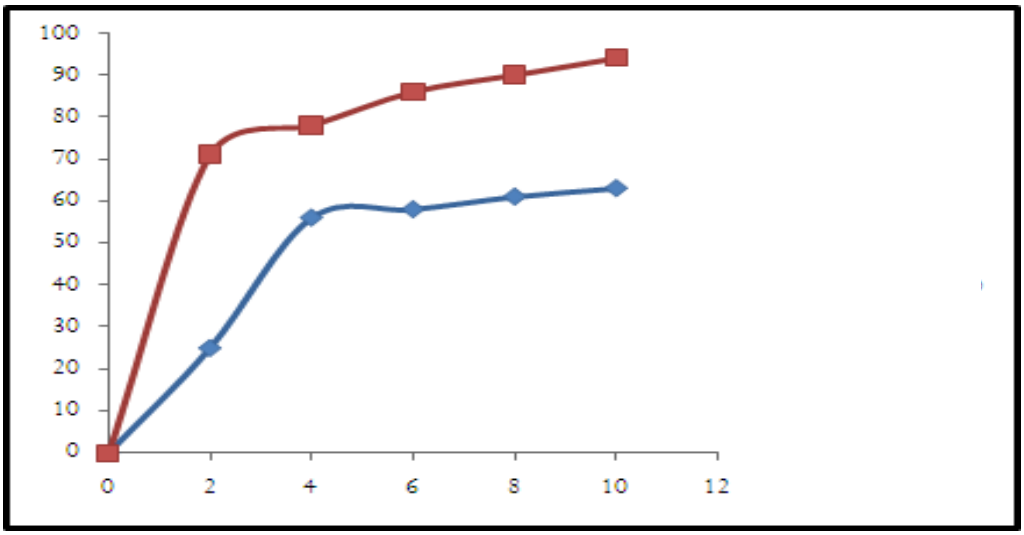


Figure 3: *In-vitro* Dissolution Study of Retrovir Vs optimized ODTs Batch F6

Table 13. 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)

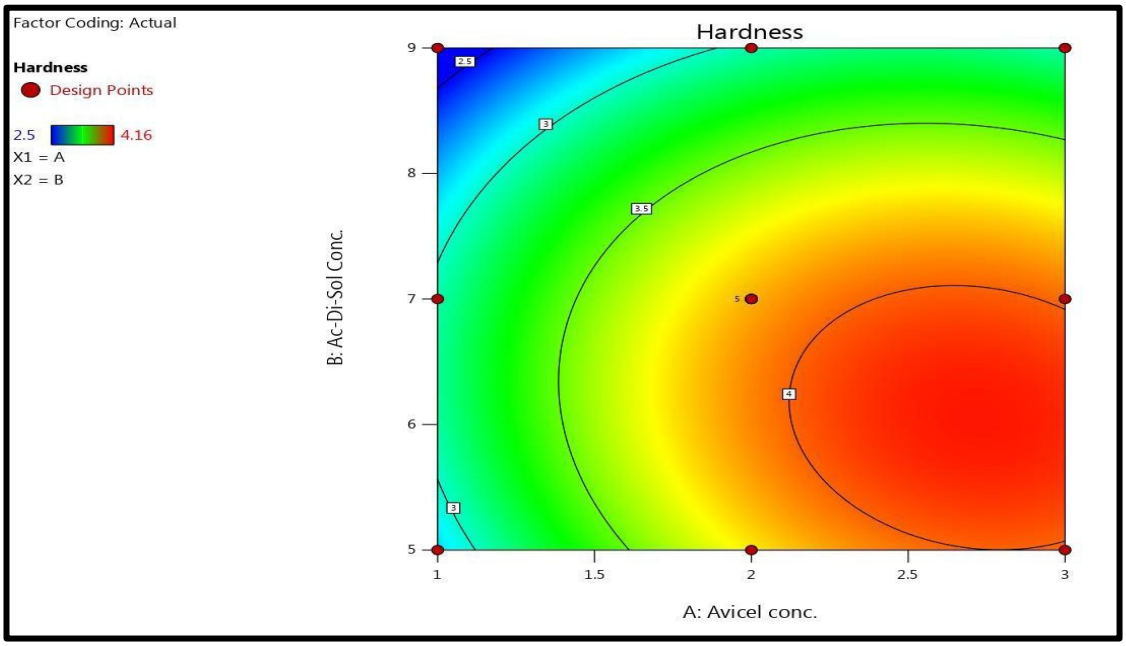


Figure 4: Interaction effect plot forhardness

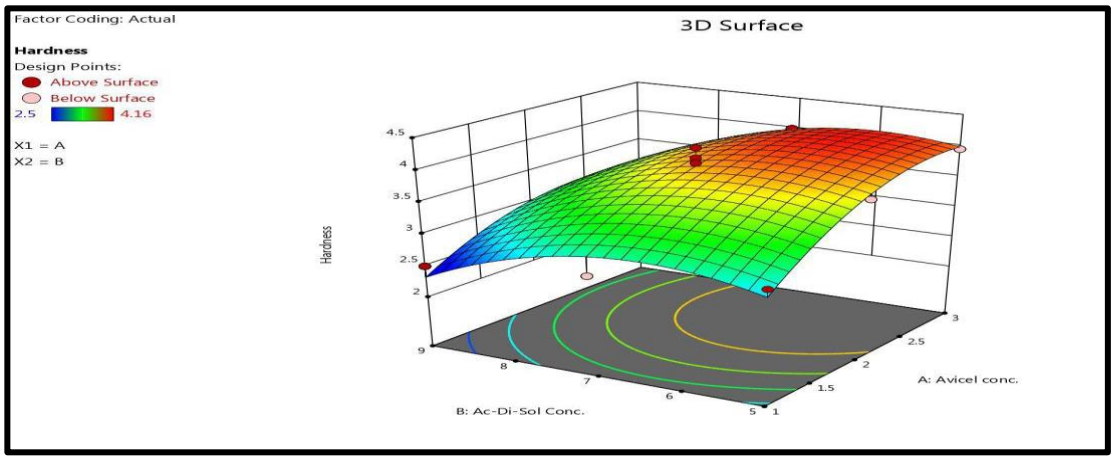
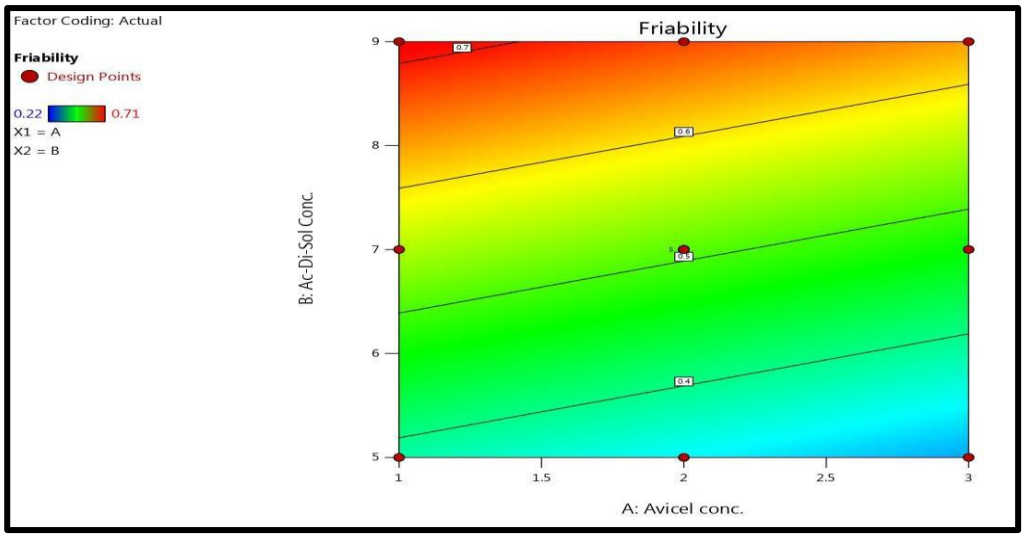


Figure 5: Response surface plot forhardness

Effect on Friability (Y2)

Figure 6: Interaction effect plot forfriability



Effect on disintegration time (Y3)

Figure7: Interaction effect plot for disintegration time

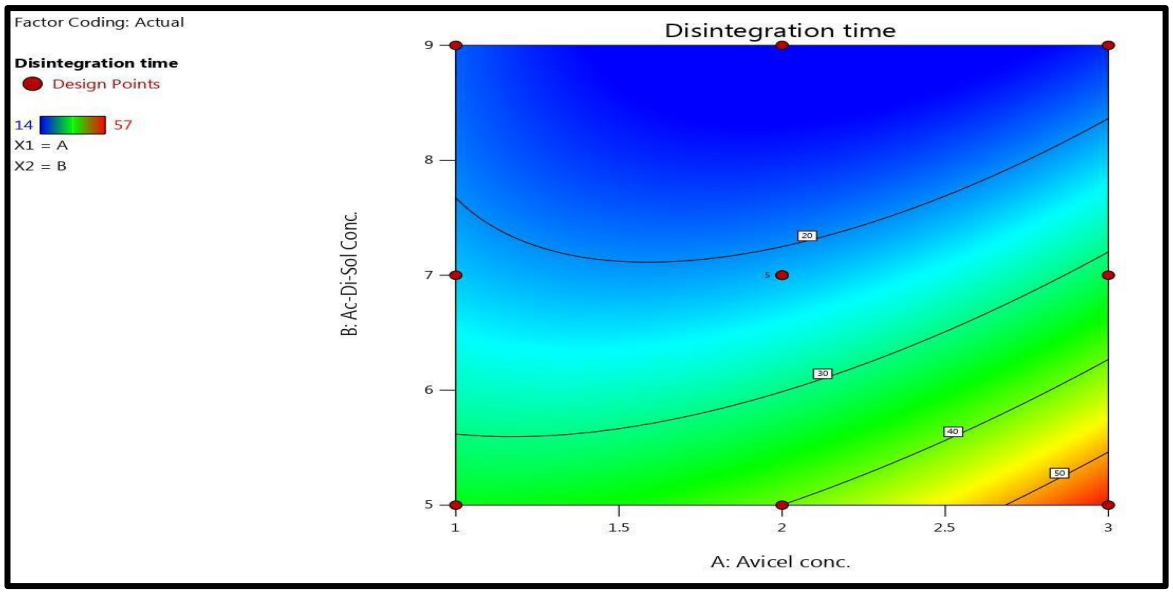


Table 14: Response coefficient table for ODTs of LMV: Indion 234 complex.

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

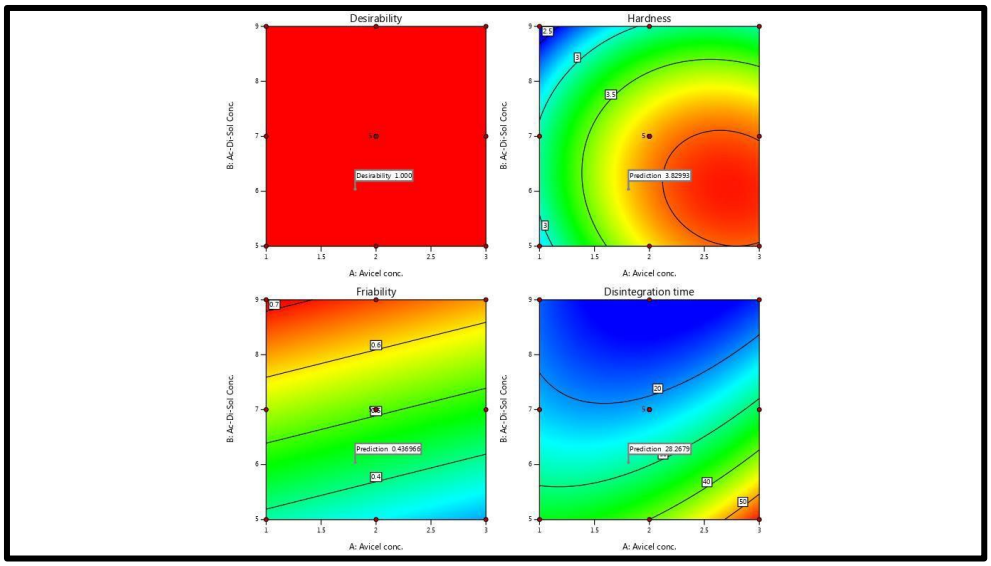


Table 15: Evaluation of Orodispersible Tablets of Vidarabine: Indion 234 Resin Complex

Test	F7	F8	F9
Weight variation test	400.0±0.89	409.4±1.11	403.2±0.94
Hardness (Kg/cm^2)	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	-	-	-
***In vivo* disintegration time (Seconds)**	47±1.84	41±1.06	50±1.37
***In vitro* dispersion time (Seconds)**	32±1.00	29±2.00	39±1.53

Table 16: 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

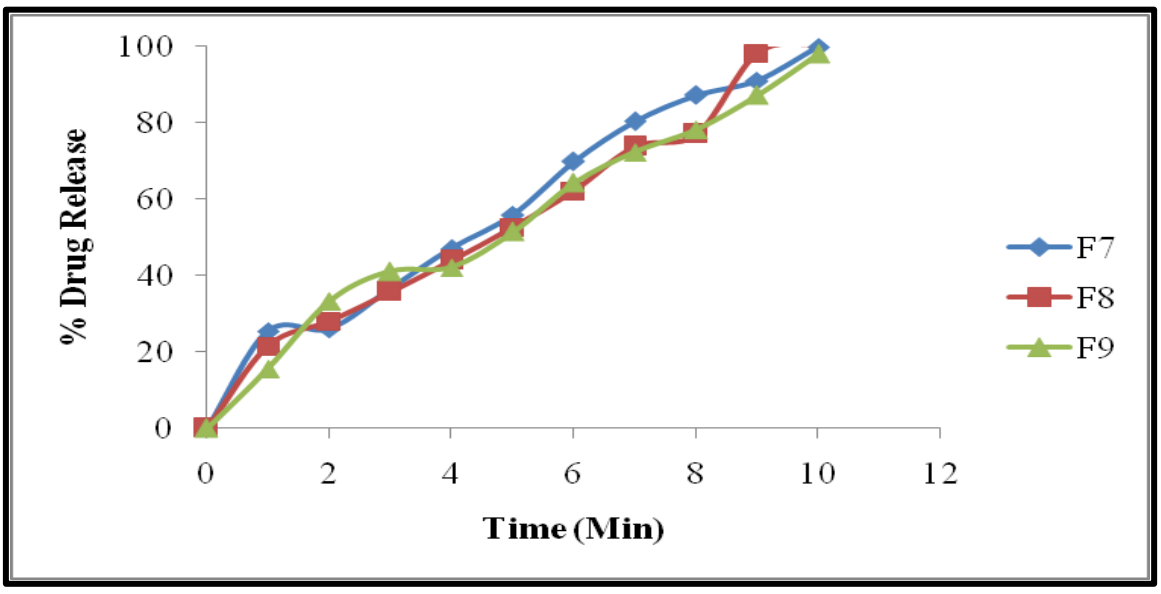


Figure 8: Dissolution profile for formulation F7, F8, F9

Accelerated Stability Studies of the OptimizedODTs.

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 $45^0C\pm2^0C$ and 75%±5%. At the end of each month, these samples were removed and analyzed for post compressiontests.

The stability analysis showed that all of the formulations were physically stable when maintained at $45^0C\pm2^0C$ and 75%±5% RH for three months, with no major differences in thefindings. (88).

Table 17: Effect of Stability Studies on ODTs Prepared by Using LMV-HP-β-CD Inclusion Complex (1:2)

Parameters Evaluated	1st month		2nd month		3rd month	
	Storage Condition		Storage Condition		Storage Condition	
	30□2⁰c/ 60□5%RH	40□2⁰c/ 75□5%RH	30□2⁰c/ 60□5%RH	40□2⁰c/ 75□5%RH	30□2⁰c/ 60□5%RH	40□2⁰c/ 75□5%RH
Hardness (kg/cm2)	4.2 □0.07	4.7 □0.18	4.0 □0.19	4.5 □0.21	4.5 □0.13	5.5 □0.19
Friability (%)	0.89	0.69	0.75	0.78	0.88	0.51
***In Vitro* Dispersion Time (sec)**	39 □0.25	42 □0.09	40 □0.18	45 □0.11	39 □0.18	44 □0.19
Drug Content (%)	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 18: Effect of Stability Studies on ODTs Prepared by Using LMV-Indion 234 Complex (1:1.5)

Parameters Evaluated	1st month		2nd month		3rd month	
	Storage Condition		Storage Condition		Storage Condition	
	30□2⁰c/ 60□5%RH	40□2⁰c/ 75□5%RH	30□2⁰c/ 60□5%RH	40□2⁰c/ 75□5%RH	30□2⁰c/ 60□5%RH	40□2⁰c/ 75□5%RH
Hardness (kg/cm2)	3.9 □0.07	4.6 □0.18	3.57 □0.19	4.2 □0.21	4.1 □0.13	5.2 □0.19
Friability (%)	0.49	0.37	0.51	0.42	0.73	0.44
***In Vitro* Dispersion Time (sec)**	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

SUMMARY AND CONCLUSION:

Oral is the most preferred route of drug administration, but is not suitable for the 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 dissolves 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-β-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-β-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 bioavailability's 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 conclude 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 treatment will allow proper formulations to be developed which in turn will improve treatment outcomes.

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