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FORMULATION OF ANTIBACTERIAL FAST DISSOLING ORAL FILMS BASED ON ISPANI SPHAGNUM PEAT WATER

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ABSTRACT

Due to the high frequency of acute respiratory desseases and particularly increased number of antibiotic-resistant strains development of antibacterial composition based on natural antibacterial component is one of the major interest for researchers. Besides fast dissolving film is an alternative form of tablet and capsule, which ensures drug systemic absroption through mucous membrane of mouth to treat respiratory desseases (pharungitis, tonsillitis, flu etc). Importance of research concernes the difficulties of swallow or chew of oral solid dosage forms by pediatric and geriatric patients. Ispani sphagnum peat water of natural origin is used as natural antibacterial component, it expresses antibacterial effect on 4 test culture: Acinetobacter spp., E. coli, S. aureus, K. Pneumonia respect. At the same time Ispani is distinguished by high content of essential elements. In the article formulation of ibuprofen and paracetamol containing fast dissoving oral film is determined. Films are prepared by solvent custing method. Optimal composition was determined based on physical and technological properties of films. Also quantitive amount of API and dose uniformity is evaluated.

KEYWORDS: Peat peloid water; Fast dissolving oral films; Disintegration time; Natural antibacterial.

INTRODUCTION

High frequency of acute respiratory desseases remains the serious problem for practical medicine, as it is the main reason for referring to hospitals. Also should be regarded the social

value of the problem, it is the serious load for country's economy, which include money spent on treatment and contemporal lack of human resources capable working. The problem is significantly actual in pediatric and geriatric practice due to their susceptibility towards desseases /5, 6, 8/.

Particularly increased number of antibiotic-resistant strains occure due to irrational use of antibiotics, what is a global problem of medicine /7, 12,18/.

Therefore, the development of antibacterial composition, using a natural antibacterial component is one of the major challenge for researchers /2, 11/.

For this reason peatland water of natural origin is used. At the same time, raw material has an important chemical properties. Ispani is distinguished by high content of essential elements. At the same time expresse antibacterial effect on 4 test culture: Acinetobacter spp., E. coli, S. aureus, K. Pneumonia respect.

For the initial therapy of nonbacterial tonzilo-pharyngitis non-steroidal anti-inflammatory drugs are used for pain relieve. And in children practice, while having sore throat and high temperature, paracetamol is recommended as first drug of choice /10, 14, 16, 17 /.

In randrom study where 8.633 patients were involved showed that ibuprofen is as well tolerated as paracetamol and in short-term treatment there was rare cases of gastrointestine side effects /3, 10/.

Besides importance of research is concerned with the difficulties of swallow or chew of oral solid dosage forms by pediatric and geriatric patients.

Development alternative dosage form of tablet and capsule such as fast dissolving films, which ensures drug systemic absroption through mucous membrane of mouth to treat respiratory desseases (pharungitis, tonsillitis, flu etc) is one of the main interest of modern science /1, 15, 19/.

The rise interest towards oral films is due to their advantages such as improved patient compliance, no need of water, fast drung absorprion may be obtained due to high vascularization of mouth mucos membrane bypassing the first-pass effect. Comparing with other solid oral dosage forms in case of oral films influenc of acid area of stomach, digestive

enzymes and secrete is avoided on active ingredient, which leads to reduction in dose and therefore side effects /9,36/.

In conclusion formulation of oral film containing natural antibacterial peat peloid water in combination with ibuprofen and paracetamol is considered to be very interesting and actual.

Experimental

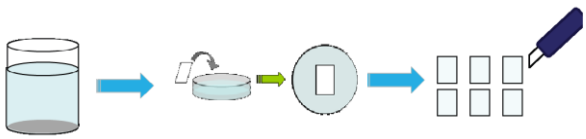
Materials

The materilas of the research: Ispani sphagnum peat water, menthol, anise oil, alcoholic extract of propolis, paracetamol, ibuprofen.

Procedure for preparation

Sample Preparation Process

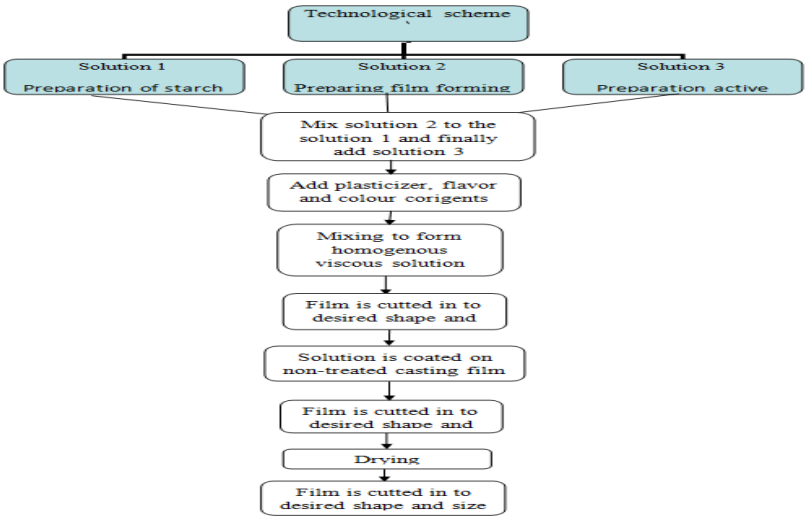
Casting method was used for preparation ibuprofen and paracetamol containing oral films.



During the experiment, the prepared samples were evaluated according the following evaluation criteria: Features, homogeneity (smooth surface, without inserts), transparency, Disintegration rate (min), plasticity, Mucoadhesive ability.

Different formulation were prepared using film forming agent, plasticizers, surfactant, thickener and stabilizers, saliva stimulating, flavoring and sweetening agen.

Samples were prepared according to the following technological scheme:



Instrumentation

Physico-chemical, technological and modern instrumental methods were used. Following instrumens were used during analyse: Analytical scale, pH-meter, magnetic stirrer, conductometer, titrator, UV-spectrophotometer.

RESULTS AND DISCUSSION

On the first stage of reasarch ibuprofen containing oral films were prepared. Composition of ibuprofen containing oral film is given in N1 table:

Table N1: Formulation ibuprofen containing oral film

Components	Formulation							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Modified starch (farinex) (g)				0,1	0,1			0,1
Ascorbic acid (g)	0,05	0,05	0,05	0,05	0,05	0,05	0,05	0,05
Limon flavouring (g)	0,01	0,01						
Raspberry Flavoring agent(g)				0,05	0,05	0,1	0,075	0,075
Red dye (g)			0,3	0,07	0,007	0,005	0,005	0,1
Sodium alginate (g)		0,3	0,3	0,3	0,15	0,175	0,15	0,15
Carboxy methylcellulose	0,3							
sucrose (g)	0,05	0,05	0,01	0,05	0,05	0,035		0,05
Anise oil (g)	0,075			0,025	0,025			
glycerol (g)	0,15	0,12	0,08	0,1	0,08			0,1
Ment oil (g)				0,05	0,05	0,075	0,075	0,05
Ibyprofen (g)	0,075	0,075	0,075	0,1	0,05	0,05	0,05	0,05
Dimethylsulfoxide (ul)							20	
Ispani peat peloid water (ml)	40	40	40	40	40	40	40	40

In order to choose the best formlulation samples were evaluated according to the following physical and technological properties shown in table №2**.**

Table №2: phisical and technological properties of ibuprofen containing films

formulation	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Film forming ability	+	+	+	+	++	+	+	++
homogeneity (smooth surface, without inserts)	-	-	-	-	-	-	-	-
transparancy	--	--	--	---	-	-	-	-
Mucoadhesive ability	+	+	+	+	+	+	+	+
Disintegration (min)	9 min	6 min	6 min	7 min	3 min	2.5 min	3 min	1.5 min
plasticity	++	++	++	+	+++	+++	+++	++++

Disintegration time of oral films depend on nature and amount of film forming agent. That's why film forming ability of polymers was studied. Besides film thickness and mucoadhesive property has direct conection with amount of film forming agent. Therefore should be

regarded that physical and chemical properties of active ingredient impact on film forming ability of polymeric substances.

Variable concentration of disintregtating agent, film forming agent, active ingredient and plasticizer has great influence on structural-mechanical properties of the films and the disintegration time.

Films formed by carboxymethylcellulose had the logest disintegration time - 9 min.

In F7 penetration enhancer, dimethylsulfoxide was added, but due to dramatically changed organoleptic characteristics it is restricted.

In F8 amount of film forming agent, sodium alginate is minimized. Amount of disintegrating agent and plasticizer provide the optimal composition of film due to the best structural properties and disintegration time.

Accordingly only F8 ibuprofen containing films were evaluated.

On the next stage of the experiment paracetamol containing films were formulated according to the technological process mentioned above.

Composition of paracetamol containing oral film is given in N3 table.

Table N3: Composition of paracetamol containing oral film

Components	Formulation								
	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}
Modified starch Farinex (g)				0,05	0,075	0,1	0,1		0,15
Ascorbic acid (g)	0,05	0,05	0,05	0,05	0,05	0,05	0,05	0,05	0,05
Raspberry Flavoring agent(g)		0,01			0,05	0,05	0,05	0,075	0,05
Red dye (g)			0,1		0,07	0,07	0,007	0,005	0,075
Sodium alginate (g)	0,3	0,3	0,25	0,3	0,3	0,4	0,25	0,1	0,2
Micro crystalline cellulose (mg)				0,05					
Carboxy methyl collulose (g)	0,1								
polyvinylpirolidone (g)				0,05	0,05				
sucrose (g)	0,05	0,05	0,01	0,05	0,05	0,05	0,05	0,05	0,05
Anise oil (g)				0,075	0,025	0,025	0,025		0,025
glycerin (g)	0,1	0,1	0,1	0,15	0,1	0,05	0,1	0,05	0,05
Ment oil (g)					0,05	0,05	0,05	0,075	0,05
paracetamol (g)	0,05	0,05	0,05	0,05	0,1	0,05	0,1	0,05	0,05
Dimethyl sulfoxide (ul)							50		
Peat peloid water (ml)	40	40	40	40	40	40	40	40	40

Prepared films were evaluated according to the following chracteristics in Table N4.

Table №4: phisical and technological properties of paracetamol containing films

formulation	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}
Film forming ability	+	+	+	++	+	++	+	+	+++
homogeneity	+	+	+	+	+	+	+	+	+
transparancy	-	-	-	-	-	-	-	-	-
Mucoadhesive ability	++	++	+	++	++	+++	++	++	+
dissolution (min)	6	3	2	5	5	2.5	4,5	2	1.5
plasticity	+	+	+	++	++	+++	+++	++	+++

Amount of disintegrant, film forming agent, active ingredients and plasticizer influence on structural-mechanical properties of films and disintegration time.

Oral film containing carboximethylcellulose as film forming agent obtained the longest disintegration time 9 min. Dimethylsulfoxide was used as penetration enhancer in F7 and F15, but due to changed organoleptic properties its usage was limited.

From the paracetamol containing formulations F17 was choosed due to its best structural properties.

That's why other quality test were checked for this formulation. Also quantivive composition of saliva stumalating agent, ascorbic acid, was determined.

On the next stage of research quality of choosed filmed were studied.

Assay of ascorbic acid: assay analyze of ascorbic acid was held according to the monograph in European Pharmacopoeia.

Table №5: Assay of ascorbic acid

#	V(ml)	Equivalent (mg)	M(mg)	M(aver. mg)	X %
1	6,125	8,81	48,552	47,791	97,10
2	5,974		47,222		94,44
3	6,017		47,600		95,20

Amount of ascorbic acid in film is 47.791 mg.

Determination of dose uniformity: Dose uniformity was derermined according to the USP Pharmacopoeia (monograph <905>).

Table №:6: determination of ascorbic acid content uniformity:

Films	**M(mg)**	48,437	48,437	47,583	44,050	49,125	44,825	47,486	44,129	43,733	48,393
	X%	**96,87**	**92,68**	**95,17**	**88,10**	**98,25**	**89,65**	**94,97**	**88,26**	**87,47**	**96,79**

Determination of paracetamol in films

Paracetamol was determined UV spectrophotometriccally at 257,0 nm wavelength. Certified paracetamol standard substance (USP - Lot: K0I244).

Table №7: Assay of paracetamol

Name	a	P	V1	L	A_0	A1	A2	K	V2	M_{mg}	M	M (%)
Oral film	20	99,8	200	10	0,7242	0,7196	0,7031	25	200	48,75	**48,57**	**97,15**
	20	99,8	200	10	0,7175		0,6980	25	200	48,40		
	20	99,8	200	10	0,7172							

Quantitive amount of paracetamol in oral film is 48,57 mg.

Determination of dose uniformity: dose uniformity of paracetmol was derermined.

Table №8: determination of Paracetamol content uniformity

Oral Films	M(mg)	48.32	47.46	49.32	48.86	45.89	47.85	43.40	45.34	46.68	47.63
	X%	96.65	94.91	98.63	97.72	91.78	95.71	86.80	90.68	93.37	95.26

Assay of Ibuprofen

Quantivive determination of ibiprofen was held according to the monograph in European Pharmacopoeia.

Table №9: Assay of ibuprofen

#	$V_{(ml)\text{-sample}}$	$V_{0(ml)\text{-Placebo}}$	Equivalent (mg)	$M_{(\%)}$	$M_{(aver.mg)}$	$X_{\%}$
1	6,320	4,033	20,63	47,181	**46,871**	**94,36**
2	6,301			46,789		**93,58**
3	6,294			46,644		**93,29**

Quantitive amount of ibuprofen in oral film is 16.871 mg.

Determination of dose uniformity: dose uniformity of ibuprofen was derermined.

Table №10: determination of ibuprofen content uniformity

Oral Films	$M_{(mg)}$	49,842	47,882	42,890	48.86	47,160	49,570	46,005	47,470	46,191	43,736
	$X_{\%}$	99,68	95,76	85,78	94,32	87,68	99,14	92,01	94,94	92,38	87,47

Disintegration: Disintegration test was held according to the pharmacopeial monograph concerning tablets. Oral films were disintegrated within 55.0-65.0 seconds.

Dissolution test: Disoolution was determined by Conductivity method /9, 13/.

Table№11: Results of dissolution test of paracetamol containing films

Sampling time (sec)	10	20	30	40	50	60	65	70	85
Water conductivity (uS/cm)	0.13								
Sample conductivity (uS/cm)	1.148	1.697	1.751	1.904	3.210	3.620	3.640	3.645	3.647

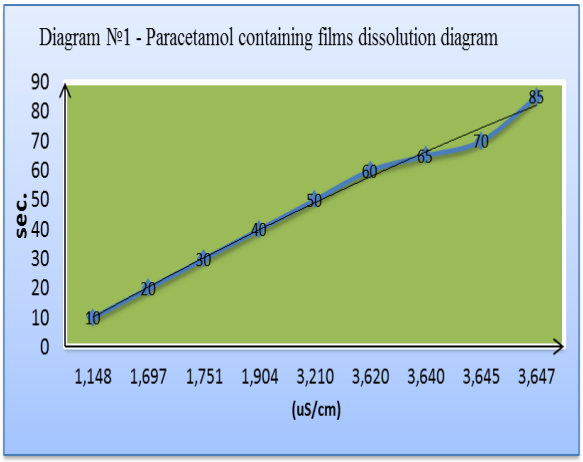
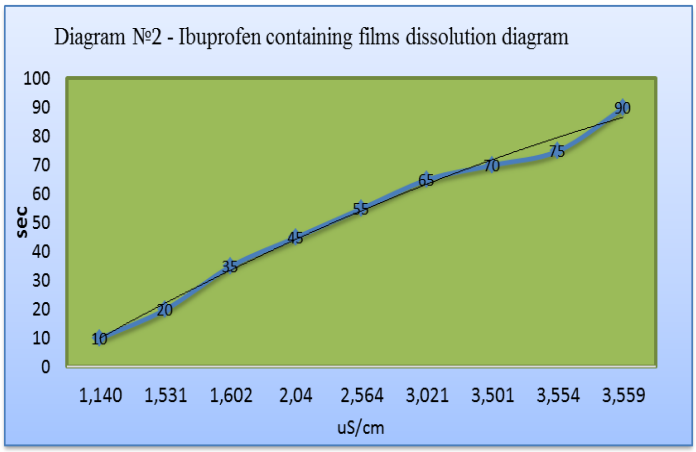


Table №12: Results of dissolution test of ibuprofen containing films

Sampling time (sec)	10	20	35	45	55	65	70	75	90
Water conductivity (uS/cm)	0.13								
Samole conductivity (uS/cm)	1.140	1.531	1.602	2.04	2.564	3.021	3.501	3.554	3.559



According to the results dissolution time for fast dissolving oral films is 85.0 – 90.0 second.

CONCLUSIONS

Ibuprofen and paracetamol containing fast dissolving oral films are formulated based on peat peloid water. Preparation technology, solvent casting method, of antibacterial and antiinflamatory oral films is determined. Physical and technological properties of films are evaluated. They perform homogenous, thin, transparent, plastic, smooth films with definite odour and smell. Disintegration time for ibuprofen and paracetamol containing fast dissolving oral films are respectively 55 and 65 second. Disolution time is 85 and 90 second respectively. Quantitive amount and dose uniformity of ascorbic acid is determined in Paracetamol containing film (results (47,791 mg) mg and (till–12,53% respectively). Amount of paracetamol is determined spectrophotometrically 48,57 mg and dose uniformity till –13,20%. Quantitive composition of Ibuprofen was determined ibuprofen containing films by acid-base titration 46,871 mg, dose uniformity is till –14,22%.

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